Sleep in depression and insomnia

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LAY OVERVIEW

Sleep disorders occur in 90% of people with depression. In the first chapter of this thesis I have reviewed the scientific literature and given a detailed background to the subject of sleep in depression and insomnia.

In the second chapter I wanted to see if one of two types of antidepressants were less disruptive to sleep particularly in the first 3 days of treatment when distress about sleep may lead to an increaesd risk of suicide. A drug known as nefazodone was shown to be less disruptive to objective sleep (measured by overnight sleep EEG,) than one called paroxetine when they were directly compared in this study.

In the third chapter I investigated the use of nefazodone in people with a history of long-term insomnia to see if it could also improve sleep in this group of people even though they did not have depression. The numbers were small but compared to placebo there was no improvement in sleep objectively or subjectively.

Psychological therapies, usually based on a cognitive behavioural model, have an important role in the treatment of depression and insomnia. Chapter 4 reports the results of a cognitive behavioural insomnia goup therapy programme set up to help people with insomnia whatever the initial cause. Results showed that although sleep times did not improve significantly patients had an improved quality of life having attended the group. In particular, participants' quality of life was improved in the domains of mental health, energy and vitality and improved perception of their general health.

ABSTRACT

This thesis explores the pharmacological and psychological treatment of both primary insomnia and insomnia secondary to depression.

The first study, in a double blind placebo controlled trial, compares the effects of two anti-depressants, nefazodone and paroxetine, on the sleep of patients with moderate to severe depression. The second study described is a cross over trial that investigates whether nefazodone compared to placebo has beneficial effects on sleep in patients with primary insomnia. The final chapter explores the treatment of primary insomnia or secondary insomnia (e.g. insomnia secondary to depression) using a cognitive behaviour therapy group approach.

In the first study, nefazodone was found, compared to paroxetine, to increase sleep efficiency, total sleep time and decrease number of awakenings as measured objectively by polysomnography. These effects were evident early in treatment, by day 3.

In the second study nefazodone was not found, compared to placebo, to increase sleep efficiency, total sleep time or decrease number of awakenings in patients with primary insomnia.

In the third study, patients with primary insomnia did report improvements in dysfunctional attitudes and beliefs about insomnia and improvements in energy/vitality and mental health, as measured by the SF36 quality of life scale, after attending group cognitive behavioural therapy (CBT). Sleep parameters were not significantly improved when compared pre and post CBT.

The findings described in this thesis have led to further work to test the efficacy of trazodone (nefazodone's sister drug) in a placebo controlled trial for primary insomnia and the continued running of the CBT insomnia group with a view to supporting patients with chronic insomnia.

ACKNOWLEDGEMENTS

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Thirdly I would like to thank both Professor David Nutt and Dr Sue Wilson who, as my academic supervisors, put their faith and trust in me. Dr Sue Wilson, an expert on sleep research and sleep disorders, was also instrumental in setting up the Bristol Insomnia Group reported on in chapter 4. She has also given me enormous assistance during the whole course of the research and writing up of this thesis.

I am grateful to Andrew Green, lead occupational therapist at the Burden Centre Frenchay Hospital, who helped run the insomnia group and has helped with the data collection for chapter 4. I would also like to thank Drs Spilios Argyropoulos, Jon Nash and Caroline Bell, and Ann Rich for their help with data collection in Chapters 2 and 3. Specifically, Dr Argyropoulos helped analyse the subjective sleep data in Chapter 2. The study in Chapter 2 was funded by Bristol Myers Squibb and Avon and West Wiltshire Pharmacy provided the medication used in Chapter 3.

Author's declaration

I declare that the work in this dissertation was carried out in accordance with the Regulations of the University of Bristol. The work is original except where indicated in the text, and was carried out with the assistance specified above in acknowledgements. No part of the dissertation has been submitted for any other degree.

Any views expressed in the dissertation are those of the author and in no way represent those of the University of Bristol.

The dissertation has not been presented to any other University for examination either in the United Kingdom or elsewhere.

Signed.....

J A Hicks

Endorsed by.....

Professor D Nutt

Head of Department

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List of Abbreviations

Ach Acetylcholine

ANOVA Analysis of Variance

ARAS Ascending reticular activating system

ASSM American Sleep Societies Meeting

BDI Beck Depression Inventory

CBT Cognitive Behaviour therapy

CGI Clinical Global Improvement Scale

DA Dopamine

DBAS Dysfunctional Beliefs and Attitudes Scale

Dep Depressed patients

DRN Dorsal raphe nucleus

DSM IV Diagnostic and Statistical Manual of Mental Disorders 4th Edition

EEG Electroencephalogram

EOG Electrooculogram

EMG Electromyogram

ESS Epworth Sleepiness Scale

GABA Gamma aminobutyric acid

HADS Hospital Anxiety and Depression Scale

5HT 5-Hydroxytryptamine

HRSD Hamilton Depression Scale

HV Healthy volunteer

ICD-10 International Classification of Diseases

ICSD International Classification of Sleep Disorders

ISQ Insomnia Symptom Questionnaire

LSQ Leeds Sleep Questionnaire

LOCF Last Observation Carried Forward

MADRS Montgomery-Asberg Depression Rating Scale

NA Noradrenaline

NAT Negative Automatic Thought

NARI Noradrenaline reuptake inhibitor

NaSSA Noradrenergic and Specific Serotonergic Antidepressant

NDRI Noradrenaline and Dopamine reuptake inhibitor

NICE National Institute for Clinical Excellence

NREMsleep Non Rapid Eye Movement Sleep

PSQI Pittsburgh sleep quality index

PSQW Penn State Worry Questionairre

PSG Polysomnogram

RCT Randomised Controlled Trial

REMsleep Rapid Eye Movement Sleep

ROL REMsleep Onset Latency

SAMI The Sleep Associated Monitoring Inventory

SARI Serotonin Antagonist and Reuptake Inhibitor

SDQ Sleep Disturbance Questionnaire

SCT Stimulus Control Therapy

SER Serotonin

SF36 Short Form 36 Questionnaire

SII Sleep Impairment Index

Slp Eff Sleep Efficiency

Sl Hyg Sleep Hygiene

SMC Self Monitoring Control

SMHSQ St Mary's Hospital Sleep Questionnaire

SMP Sleep Misperception

SNRI Selective Noradrenaline Reuptake Inhibitor

SRT Sleep Restriction Therapy

SOL Sleep Onset Latency

SSRI Selective Serotonin Reuptake Inhibitor

SWS Slow Wave Sleep

STAI State Trait and Anxiety Inventory

TCA Tricyclic antidepressant

TCQI-R Thought Control Questionnaire Revised

TMN Tuberomamillary nucleus

TST Total Sleep Time

VPLO Ventro lateral preoptic nucleus

vPAG Ventral periaqueductal grey matter

CONTENTS

Chapter 1.

Background to Sleep in Depression and Insomnia

1.1 Introduction

"From nearly all social history and biography, one third of the story is missing a gap of about eight hours in every day, hours which need by no means be uneventful or without significance."

"History of the Bed" Wright

1962[1]

There has been much published on the biological and psychological aspects of sleep, but it is only recently that sleep has been looked at in a sociological framework. Williams and Bendelow[2] argue that sleep entitles people to expect certain rights. These include: freedom from noise and interference from others, except in emergencies; exemption from normal role obligations; and retention of the status and authority associated with daytime roles. They also contend that sleep is socially patterned, reflecting the social roles, responsibilities and gender relationships inherent in our daily lives.

In 2003 Hislop and Arber [3 4] carried out the first study of mid life women aged 40-59, to address the sleep pattern of women within their social context. At mid life women often have multiple roles. They may be the mothers of young children and/or teenage

or adult children, with each phase of motherhood with its unique demands and responsibilities impacting on women's sleep. As well as experiencing the physiological symptoms of the menopause, midlife women may be re-entering the workforce on a full time basis after parenting, and holding responsible positions with increased stress and pressure. They may be supporting partners through periods of work place change, redundancy and early retirement, or suffering the effects of broken relationships. As daughters of ageing parents they may have increased caring responsibilities and the stresses of bereavement.

Hislop and Arber collected qualitative data from focus groups and audio sleep diaries.[3]

Results showed that in sleep, women are first and foremost partners and/or mothers and the performance of physical and emotional labour required by these roles often curtails their right to a good night's sleep. They see disturbed sleep as a "women's lot" but they appear to accept that their partners and children will act as gatekeepers at times blocking their access to sleep. Instead of seeing themselves as victims they seek pragmatic solutions within the constraints of their social context which balance the demands of their responsibilities within the household with their need for sleep.

Currently there are studies being carried out to address the sociology of men's sleep particularly in the context of measuring how couples sleep.

1.2 Normal sleep

Sleep is comprised of two distinct physiological states. These are rapid eye movement (REM) sleep and non rapid eye movement (non REM) sleep. Rechtshaffen and Kales

(1968) with the American Government Health Office published a manual produced by a committee of experienced health researchers to 'stage' human sleep. They are known universally as the "Rechtshaffen and Kales criteria", standardise sleep scoring and are used worldwide by most sleep researchers.[5] There are however limitations of the criteria, as they were defined for normal subjects who are not taking medication, and so are more difficult to apply to patients with sleep disturbance such as in depression and due to psychotrophic medication. For example, depressed patients have less well defined sleep spindles and less obvious sleep stages (see below).

Non REM sleep is made up of four stages: Stage 1 is a light drowsy phase during which there is a transition from wakefulness to sleep. The normal rhythms of the waking electroencephalogram (EEG), alpha (8-13) Hz and mixed fast activity (14-30) Hz are replaced by theta activity (4-7) Hz. Slow rolling lateral eye movements can also be picked up on the electro-oculogram (EOG). Stage 2 is the first unequivocal stage of sleep with the appearance of sleep spindles (widespread runs of 12 -14 Hz activity) and K complexes (large biphasic slow transients) in the EEG and normally eye movements are absent. Stages 3 and 4 are known collectively as Slow Wave Sleep (SWS) characterized by synchronised delta or slow activity (0-4Hz). If the activity is below 2Hz, of an amplitude greater than 75 microvolts and occupies 20%-30% of the epoch (conventionally a 30 seconds time period) then it is deemed to be stage 3 sleep. If this activity occupies 50% of the epoch it is stage 4 sleep.

REM sleep has an EEG pattern of low amplitude and mixed frequencies similar to waking or stage 1 sleep with occasional sharp transients interspersed. There is

complete lack of muscle tone but occasional phasic muscle twitches. It is also characterised by frequent jerky conjugate eye movements, which can be lateral or vertical (Figure 1.1).

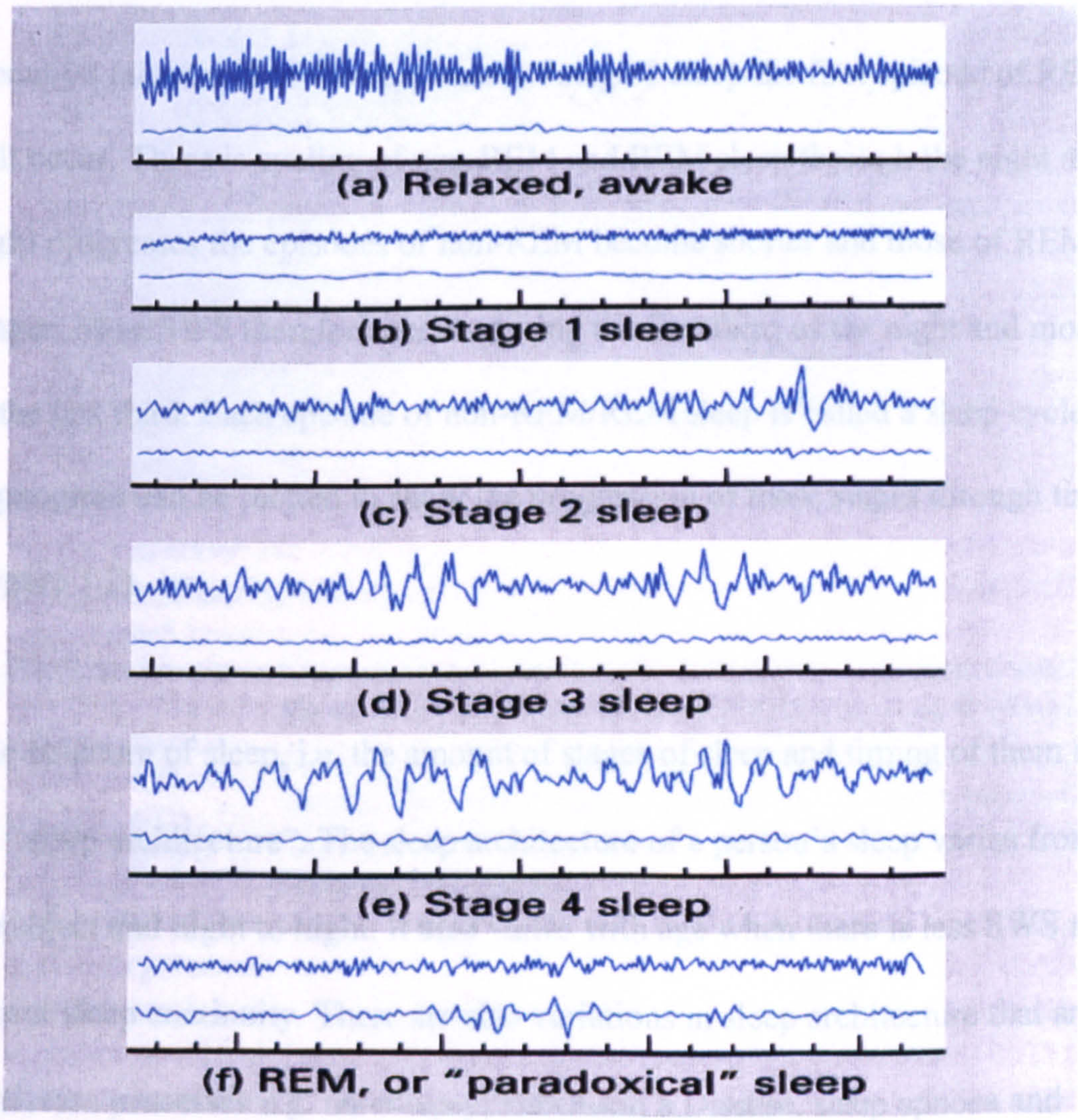


Figure 1.1: Tracings depicting the different stages of sleep. Top line in each trace represents scalp EEG electrode and the bottom line represents eye movement.

As people fall asleep they progress through the non-REM stages. Stage 1 is the stage of drowsiness and together with waking is a measure of poor sleep continuity. People who wake when they are asleep usually deny being asleep if it is from stage 1.[6] Stage 2 is light sleep from which it is fairly easy to wake subjects. Myoclonic jerks and

'falling' arousals occur in this stage and about 50% is spent in this stage. In SWS stage 3 and 4 people are pale and still with a slow regular heart rate and breathing. If someone is woken from slow wave sleep the person will feel groggy and confused.

About 90 minutes later than the onset of stage 1 sleep the first episode of REM sleep will occur. There is cycling of non-REM and REM sleep through the night and as the night progresses the episodes of non-REM become shorter and those of REM become longer. Most SWS therefore occurs during the first third of the night and most REM in the last third. Each episode of non-REM/REM sleep is called a sleep cycle and a hypnogram can be plotted to show the progression of these stages through time (Figure 1.2).

The structure of sleep, i.e. the amount of stages of sleep and timing of them is known as "sleep architecture". The sleep architecture of a person's sleep varies from subject to subject and night to night. It also varies with age when there is less SWS and poorer sleep continuity. There are also variations in sleep architecture that are related to disease processes e.g. narcolepsy, Parkinson's Disease, sleep apnoea and psychiatric problems e.g. depression and the taking of medication.[7] There are also sleep architecture changes in insomnia.

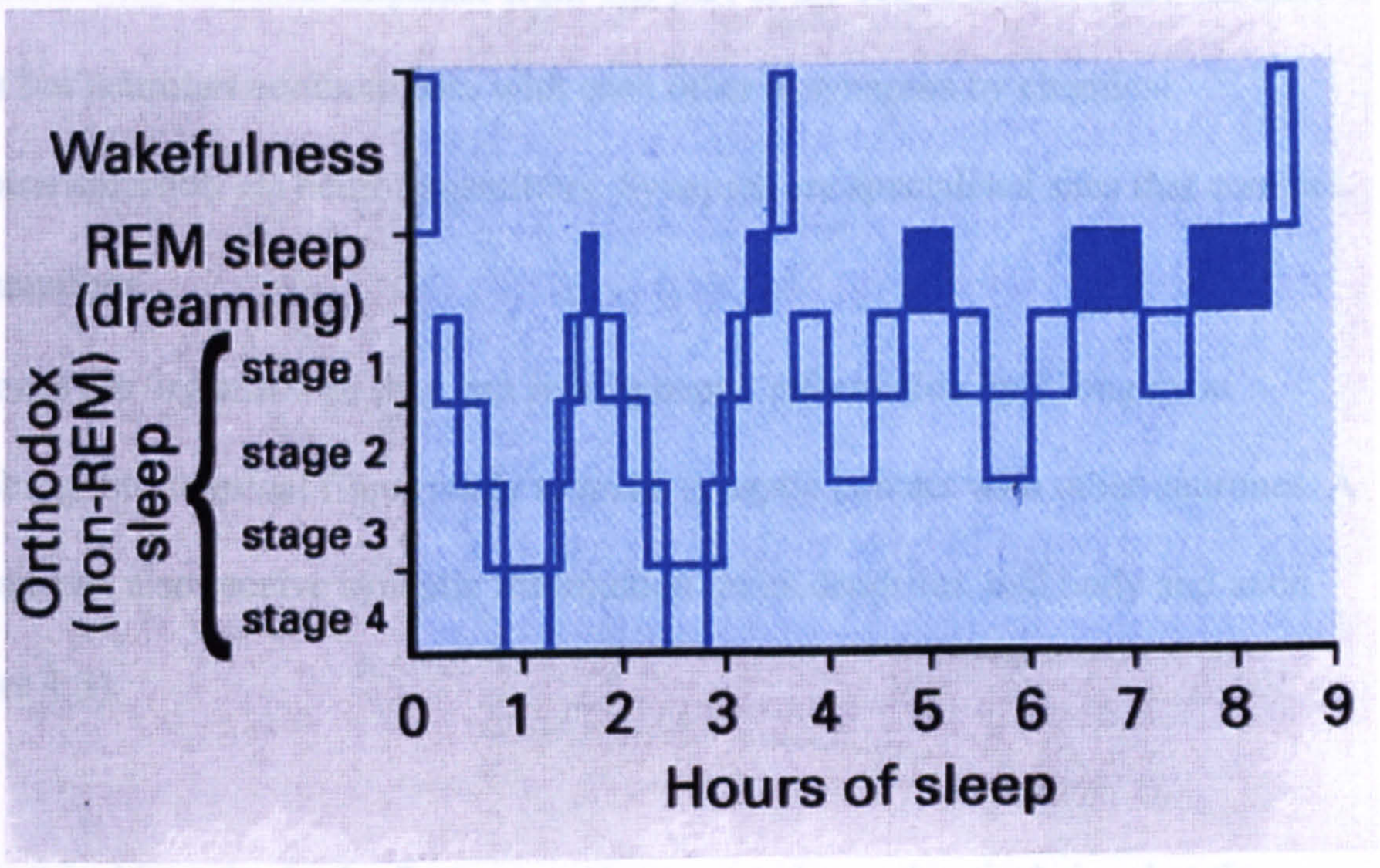


Figure 1.2: **Hypnogram showing the progression of sleep stages through time, with cycles of REM and non-REM sleep. The duration of each cycle is approximately one and a half hours. Slow wave sleep dominates the early part of sleep whereas REM sleep is more predominant in the latter stages of the night.**

1.3 Introduction to neurotransmission

In order to understand what is known at a molecular level about sleep, and the effect of drugs on sleep, a basic understanding of the psychopharmacology of neurotransmission is important. There are many neurotransmitters in the brain but some of the most important are 5-hydroxytryptamine (5HT) or serotonin, noradrenaline (NA), Acetylcholine (ACh), gammabutyric acid (GABA)- inhibitory and glutamate-excitatory.

Neurones send electrical impulses from one part of the cell to another part via their axons but neurones communicate with each other at synapses by chemical neurotransmission via neurotransmitters. Synapses are specialised sites that connect two neurones.

Neurones are organised so they can send synaptic information by a long axon branching into terminal fibres ready to make synaptic contact with other neurones. A neurone can also receive synaptic information on its dendrites, cell body and axon (Figure 1.3).

An electrical impulse in the first neuron is converted to a chemical signal at the synapse by a process known as excitation–secretion coupling. Once an electrical impulse invades the presynaptic axon terminal in the first neuron it causes release of the chemical neurotransmitter stored there. This release of neurotransmitter, the first messenger, shoots across the synapse and hits target sites on the postsynaptic receptor very selective for that neurotransmitter. This opens a process that converts the chemical message back to an electrical impulse in the second nerve, or starts other biochemical processes within the post synaptic neuron, (via second messengers.)

Changes in the rate of receptor synthesis can powerfully modify chemical neurotransmission at the synapse. When fewer neurotransmitter receptors are formed "down regulation" occurs and when more neurotransmitter receptors are formed "up regulation" occurs.

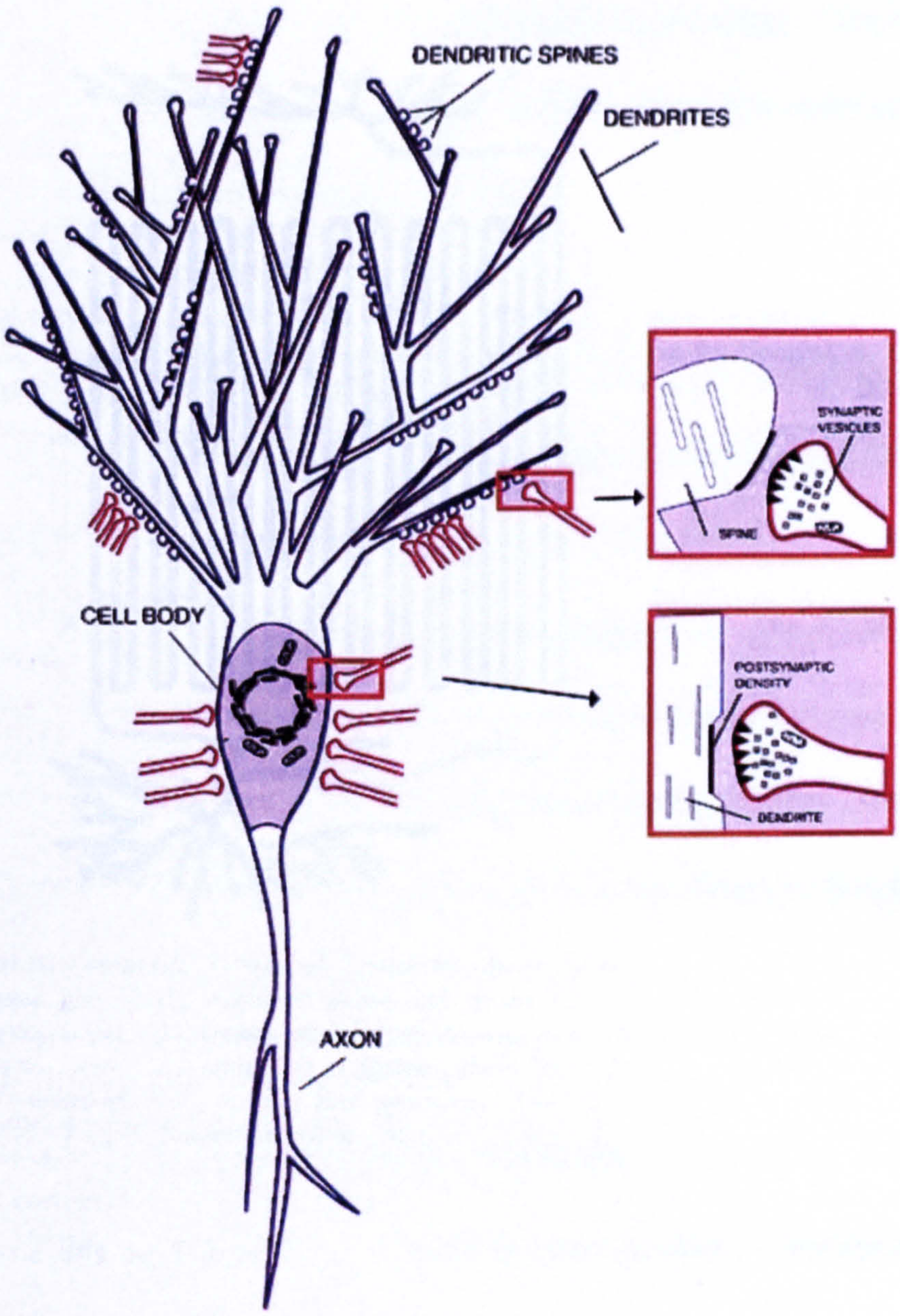


Figure 1.3: **This figure shows how a neuron is organised to receive synaptic information. Pre-synaptic input from other neurons can be received post-synaptically at many sites, but especially from dendrites, often at specialised structures called dendritic spines. Other post-synaptic neuronal sites for receiving pre-synaptic input from other neurons include the cell body and axon.**

Enzymes involved in neurotransmission can be inhibited by some drugs. This can be reversible or irreversible. If it is irreversible enzyme activity cannot be restored unless another molecule of enzyme is synthesised by the cell.

Naturally occurring neurotransmitters stimulate receptors. These are called agonists. Some drugs do stimulate receptors just like the natural neurotransmitter and are also therefore agonists. Other drugs actually block the actions of the natural neurotransmitter at its receptor and are therefore called antagonists. Antagonists only exert their actions in the presence of agonists but have no activity of their own in the absence of agonists. Other drugs do the opposite of agonists and are called inverse agonists. Partial agonists and partial inverse agonists also occur. There is therefore a spectrum for drugs acting at a receptor (Figure 1.4).

Figure 1.4: The Agonist Spectrum

Agonist **Partial Agonist** **Antagonist** **Partial Inverse Agonist** **Inverse Agonist**

In the central nervous system neurones exist specifically for the neurotransmitters 5-hydroxytryptamine (5HT), Noradrenaline (NA), Dopamine (DA), Acetylcholine (ACh). In the brain NA and 5HT neurones are located in brain stem structures such as the raphe nucleus and the locus coeruleus with projections to the frontal cortex. There are however also many different receptor subtypes for each of these neurotransmitters. The main subtypes are summarised in Table 1.1.

Transmitter	Pre synaptic	Post synaptic
NA	alpha2 blocked by mianserin, mirtazepine	alpha1 alpha2 beta1 beta2
DA		DA1, DA2.....
5HT	5HT1A, blocked by nefazodone and trazodone 5HT1B 5HT1D	5HT1A, 5HT1D, 5HT2A blocked by nefazodone, trazodone, mianserin, mirtazepine, trimipramine, amitryptiline, 5HT2C 5HT3 5HT4.
ACh		Nicotinic Muscarinic

Table 1.1: Subtypes of neurotransmitter receptors in the brain

1.4 Function of sleep

The precise function of human sleep is unknown however there have been a number of theories proposed. Conservation of energy, and a period of recuperation or restoration theories have been postulated.[8] The theories overlap.

Slow Wave Sleep

(i) "Conservation of energy theory"

SWS is probably involved in a homeostatic process. Most people's general activities increase during the day compared with the night. The concept of homeostasis may be extended to explain that energy that is expended during the day must be balanced by a recuperative period. This forms the foundation of one of the theories of the function of sleep, that of conservation of energy. Oxygen consumption, heart rate and body temperature decline during the first few hours of sleep. Energy expenditure can be

measured by metabolic rate which is raised by the day and reduced during the night, particularly in SWS, by 5-25%.[8] The level of SWS is highest in young individuals who are most active.

(ii) "Restoration of energy theory"

Sleep is postulated to be a process by which the whole body, including the central nervous system can be restored. SWS is linked to anabolic processes. Paradoxically anabolism therefore occurs during a period of relatively low oxygen consumption and lowered metabolic rate. Growth hormone is released at night particularly in SWS.[9] When the need for growth is great both the duration of slow wave sleep and the overall amount of sleep is increased supporting the restorative function of SWS. Table 1.2 summarises some of the evidence for the restorative function of SWS.

Two processes interact in normal sleep.[10] The sleep homeostat "drives" the sleep-wake schedule toward a balanced requirement because prolonged wakefulness accrues sleep debt and sleep pays off the debt and the circadian timer regulates the biological clock in approximation to the 24hr clock. This is hypothesised to be via "Process S" which is a substance that accumulates in the brain during the day and declines exponentially with sleep and the circadian influence "Process C".

Also the cycling of non-REM and REM sleep may be fundamental to the restoration accomplished during sleep. Each sleep cycle results in partial restoration and after a number of cycles recuperation is complete which reduces the need for SWS or "core sleep." This may explain why the duration of SWS reduces during the course of a night's sleep as "optional sleep" governed by circadian factors continues.

At a molecular level in the brain, postsynaptic receptors of the 5HT2 type are thought to be involved in the control of SWS. A selective 5HT2A antagonist, ritanserin was found to increase SWS in healthy volunteers[11] and mCPP, an agonist with its highest affinity at 5HT2C receptors, decreases it.[12] Sharpley (1994)[13] used ketanserin a 5HT2A antagonist, with a lower affinity for 5HT2C receptors than ritanserin and found ketanserin was much less effective than ritanserin in increasing SWS. They suggest that 5HT2C receptors may therefore be more strongly implicated in the regulation of SWS than 5HT2A receptors.

Rapid Eye Movement sleep

It has been suggested that during REM sleep neuronal connections in the catecholamine system are formed and that this activity is necessary to maintain cognitive function. Decreasing acetylcholine function generally decreases REM sleep. At a molecular level there is evidence that the neurons which initiate the onset of REM sleep in the final pathway are actually cholinergic i.e. release ACh but they are influenced by noradrenergic neurones.[14-17] The cholinergic neurones appear to initiate downward inhibitory impulses that cause atonia during REM sleep and the upward processes that stimulate cortical arousal and the phasic events of REM.

The disruption of sleep e.g. by the many causes of insomnia will therefore interrupt the restorative function of sleep and effect the quality of sleep. This may be as important as disruption in sleep continuity.

Raised metabolic activity associated with increased TST and SWS:	**Decreased metabolic activity associated with decreased SWS**
Pregnancy	Blind Patients
Exercise	Quadraplegic patients
Sleep deprivation	
Adolescence	
Hyperthyroidism	Hypothyoidism
Refeeding of patients with anorexia	
During the mounting of an immune response	
Increased levels of cell division and protein synthesis Brain restoration as opposed to body restoration	

Table 1.2: Metabolic activity and Slow Wave Sleep

1.5 Sleep Circuitry

Sleep wake behaviour is sub-served by a number of brain regions, cell types and extracellular messengers making up an elaborate circuit within the brain. The ascending reticular activating system (ARAS) which originates in the rostral pontine reticular formation and passes through the midbrain reticular formation to the thalamus was identified in the 1950's, and associated with arousal.[18]

Different cholinergic and monoaminergic brainstem neurones with projections to the cerebral cortex and elsewhere in the brain were identified during the 1970's and 80's and as above, cholinergic neurones were associated with REM sleep and monoaminergic neurones exhibited their highest activity in NREM sleep and waking (Table 1.3).

Dorsal and medium raphe (DRN and MnRN)	serotonin
Midbrain	dopaminergic
Laterodorsal/pedunculopontine tegmental LDT/PPT	cholinergic
Locus coeruleus LC	noradrenergic
ventral periaqueductal grey (vPAG),	dopaminergic
tubermamillary nucleus neurons (TMN)	histaminegic and GABA

(Projections ascend to the thalamus, cerebral cortex, lateral hypothalamus and basal forebrain.)

Table 1.3 The main brain-stem neurones and their neurotransmitters

Most recently, attention has focused again on the hypothalamus and the ventrolateral pre-optic nucleus (VLPO) being proposed as a "sleep centre" and the hypocretin/orexin cells of the perifornical area and their projections being a "waking centre." The data from these and other regions associated with the sleep wake cycle have led to the "flip-flop switch model of sleep-wake control" in which two sets of mutually inhibitory neurons make sharp state transitions and hence may explain the suddenness of falling asleep or waking up.[15] The sleep side is thought to be the VLPO and the arousal side includes the tubermamillary nucleus, histaminegic neurons (TMN), dorsal raphe (DRN) serotonergic neurons, ventral periaqueductal grey (vPAG), dopaminergic neurons and locus coeruleus (LC) noradrenergic neurones. The VLPO does not have orexin receptors so they are not part of the switch but loss of the orexin neurones weakens the arousal side of the switch because they have an excitatory effect on the neurons above.

The ARAS is now proposed to be involved in the maintenance of consciousness whereas the VPLO that runs in parallel with the ARAS controls sleep.

Some hypnotic drugs may exert their effects in a regionally specific manner e.g. gaboxadol, a GABA receptor agonist, through activation of the VLPO. This may lead to the development of further hypnotic drugs, which exert their effects via the VLPO.

1.6 Sleep in depression

Sleep abnormalities in depression are well established. Insomnia is the most common complaint although hypersomnia is the dominant sleep abnormality in approximately 30% of depressed patients.[19] Insomnia in depression is reported clinically as sleep initiation and continuity difficulties. These include difficulties falling to sleep, known as prolonged sleep onset latency (SOL), intermittent wakefulness during the night, and early morning waking (EMW), typically at 3-4am. Table 1.4 and Figure 1.5 show sleep architecture changes in a depressed patient and a hypnogram of a depressed patient.

Over 90% of patients with major depression have sleep complaints.[19] Persistent sleep disturbance is related to a significant risk of relapse and recurrence of depression and risk of suicide.[20]

REM sleep abnormalities, rather than SWS changes, are the more robust findings in depression with the time taken to enter the first REM period (REM onset latency) being shortened as the most consistent finding although REM density is also increased compared to controls in some depressed patients.[21] REM onset latency increases with age and severity of the depression and is particularly shortened in endogenous depression.

Non REM sleep

Decreased SWS
Decreased SWS in Non REM-1 versus Non REM-2
Increased Stage 1 sleep

REM sleep

Reduced REM latency
Increased REM during the first half of the night
Increased REM density

Table 1.4: Polysomnogram (PSG) abnormalities in depression showing abnormal sleep architecture (Reynolds and Kupfer 1987[22])

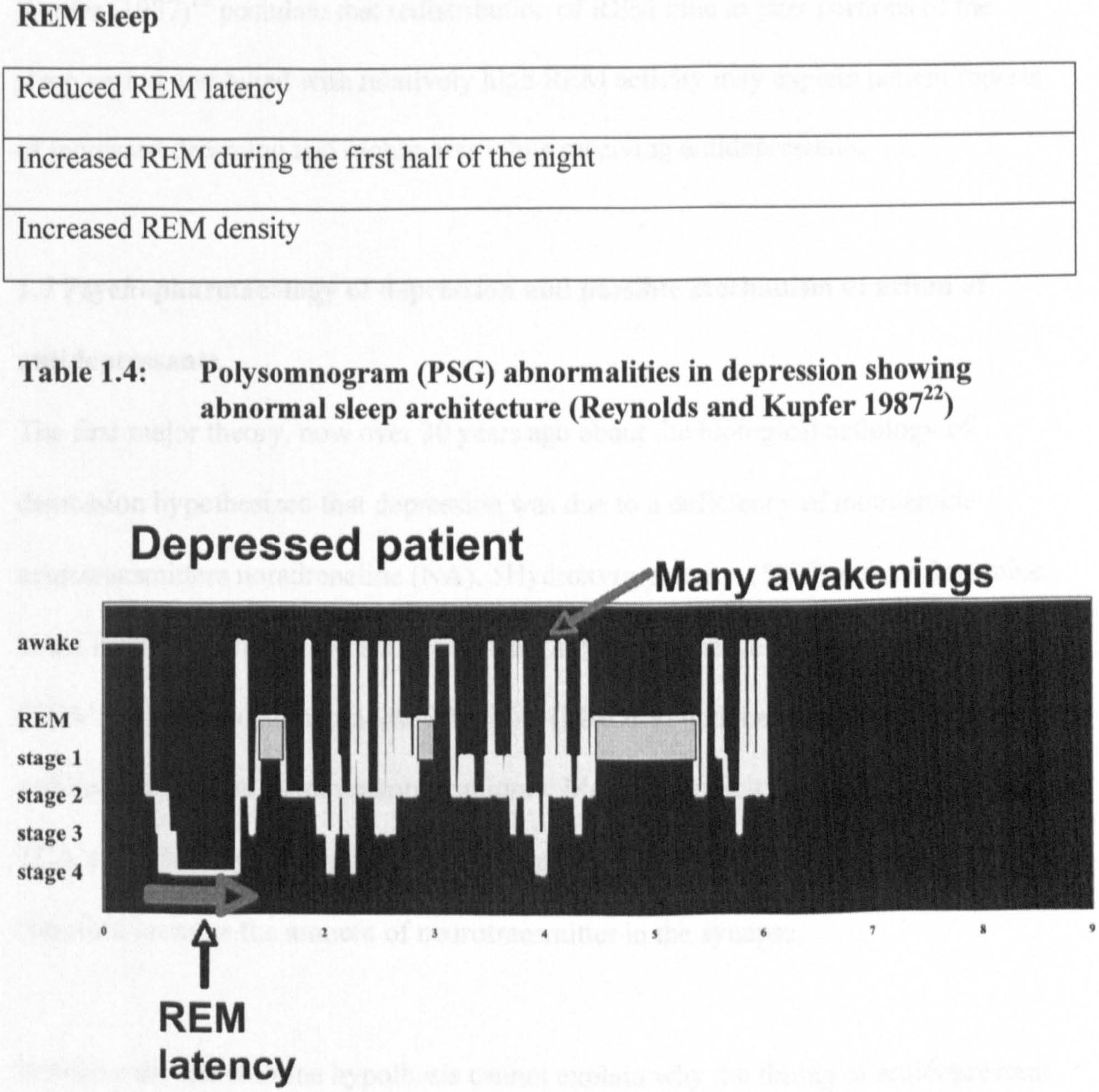


Figure 1.5: Hypnogram of a depressed patient

The persistence of a depression-like sleep pattern in fully remitted depressed patients suggests that as well as being a "state marker," REM abnormalities are also a "trait marker." The EEG sleep patterns of subjects without a personal history but with a strong family history of depression differed from those of controls showing a depression like pattern with less SWS and increased REM density.[23] Reynolds and Kupfer (1987)[22] postulate that redistribution of REM time to later portions of the sleep period combined with relatively high REM activity may explain patient reports of increased dreaming and nightmares while receiving antidepressants.

1.7 Psychopharmacology of depression and possible mechanism of action of antidepressants.

The first major theory, now over 30 years ago about the biological aetiology of depression hypothesized that depression was due to a deficiency of monoamine neurotransmitters noradrenaline (NA), 5Hydroxytryptamine (5HT) and /or dopamine in the brain.[24 25] The known antidepressants at this time tricyclic antidepressants (TCA'S) and monoamineoxidase inhibitors (MAOI's) both had pharmacological actions that boosted these neurotransmitters. MAOI'S, inhibit the enzyme MAO, TCA's and 5HT inhibitors block monoamine reuptake transporter pumps and therefore increase the amount of neurotransmitter in the synapse.

However the monoamine hypothesis cannot explain why the timing of antidepressant effects on neurotransmitters is different from the timing of antidepressant effects on mood. Antidepressants boost monoamine immediately although their antidepressant

effect takes 2-3 weeks to appear. It is now thought that changes in neurotransmitter receptor sensitivity are necessary to mediate the clinical response and the time for the neurotransmitter receptor to down regulate and desensitize therefore delays the therapeutic effect. Figures 1.6-1.11 illustrate the monoamine hypothesis of depression with up regulation and down regulation.

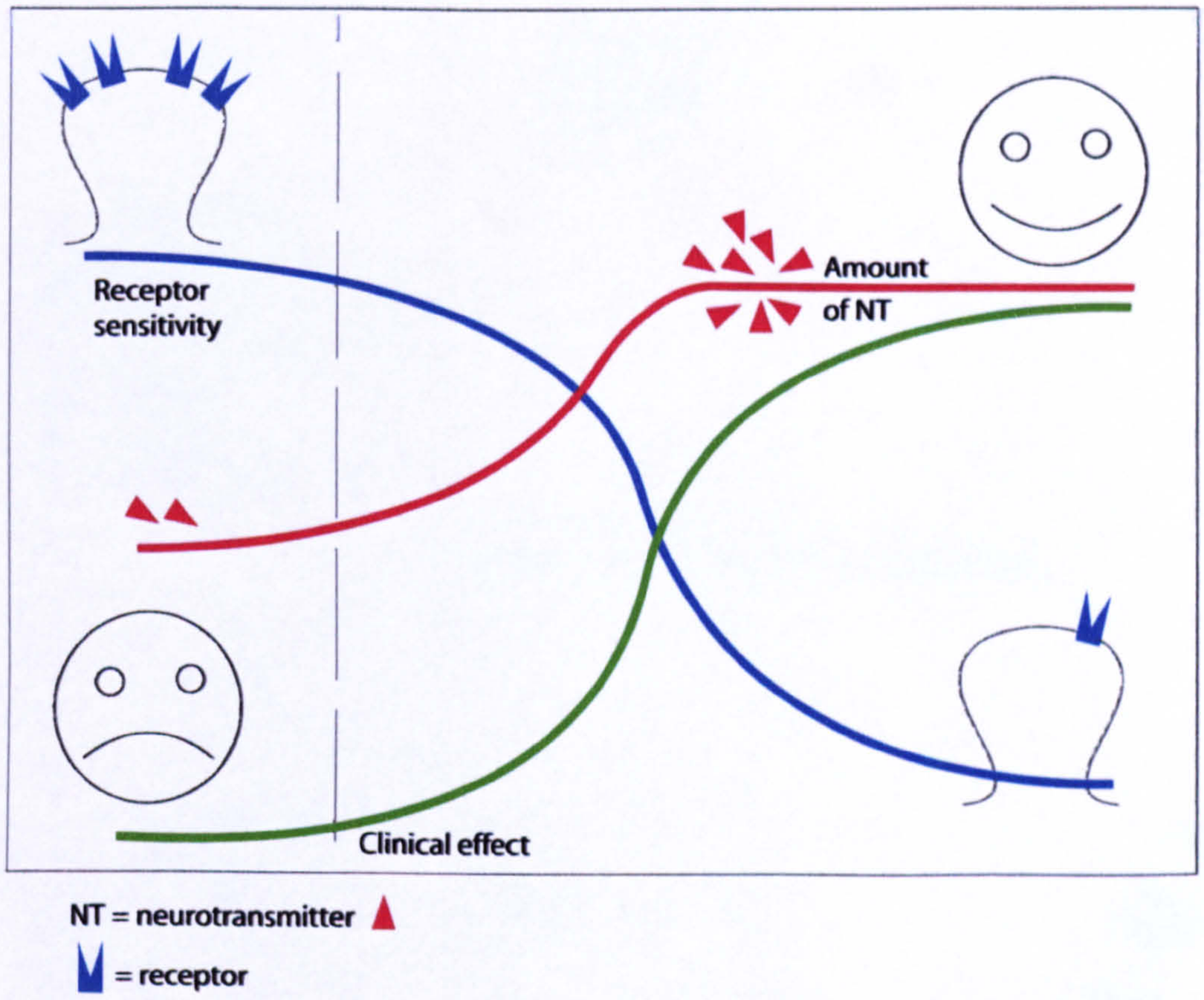


Figure 1.6: Different time courses for three effects of antidepressant drugs, changes in mood, changes in neurotransmitters and changes in receptor sensitivity.

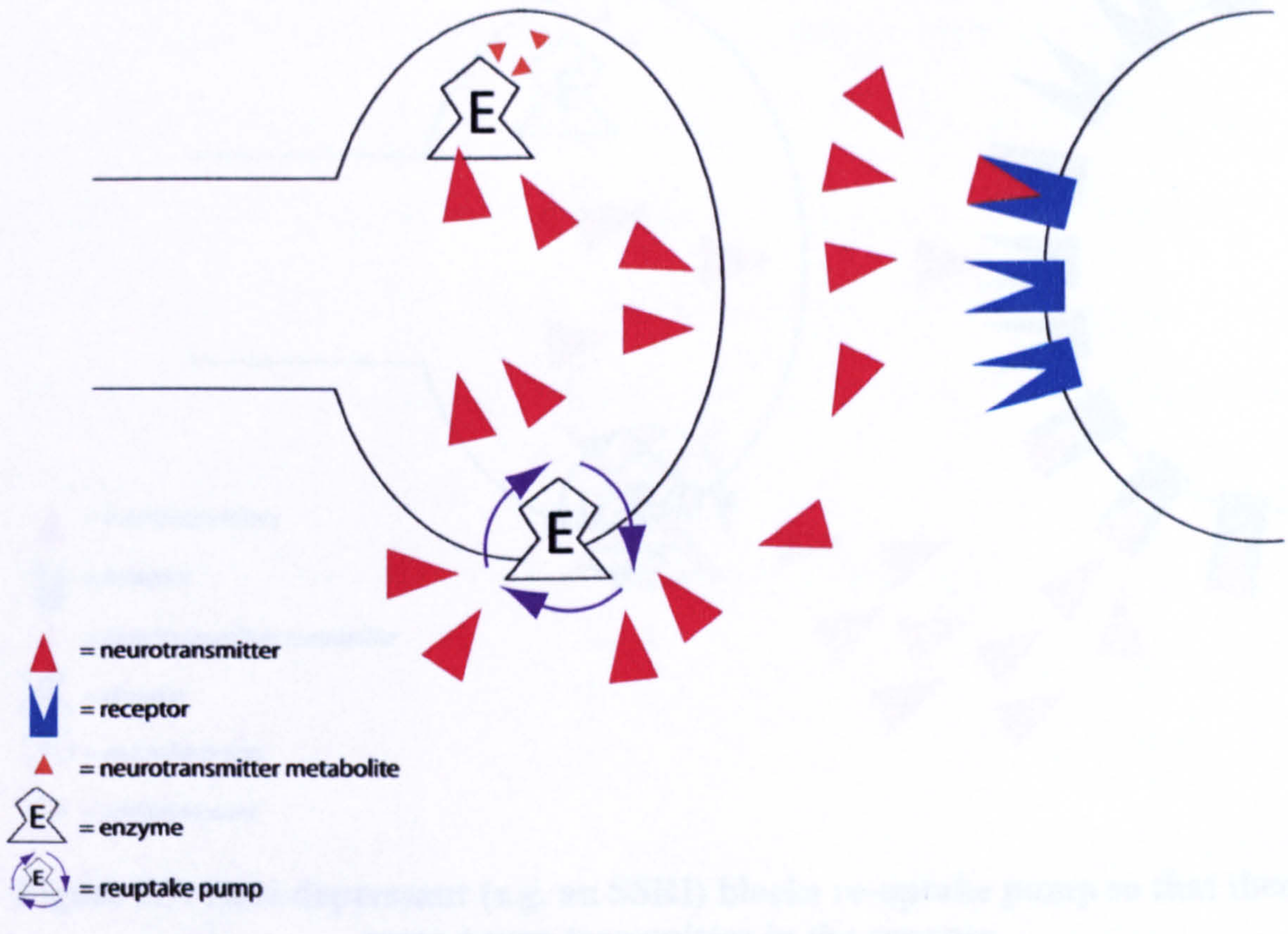


Figure 1.7: Normal Functioning

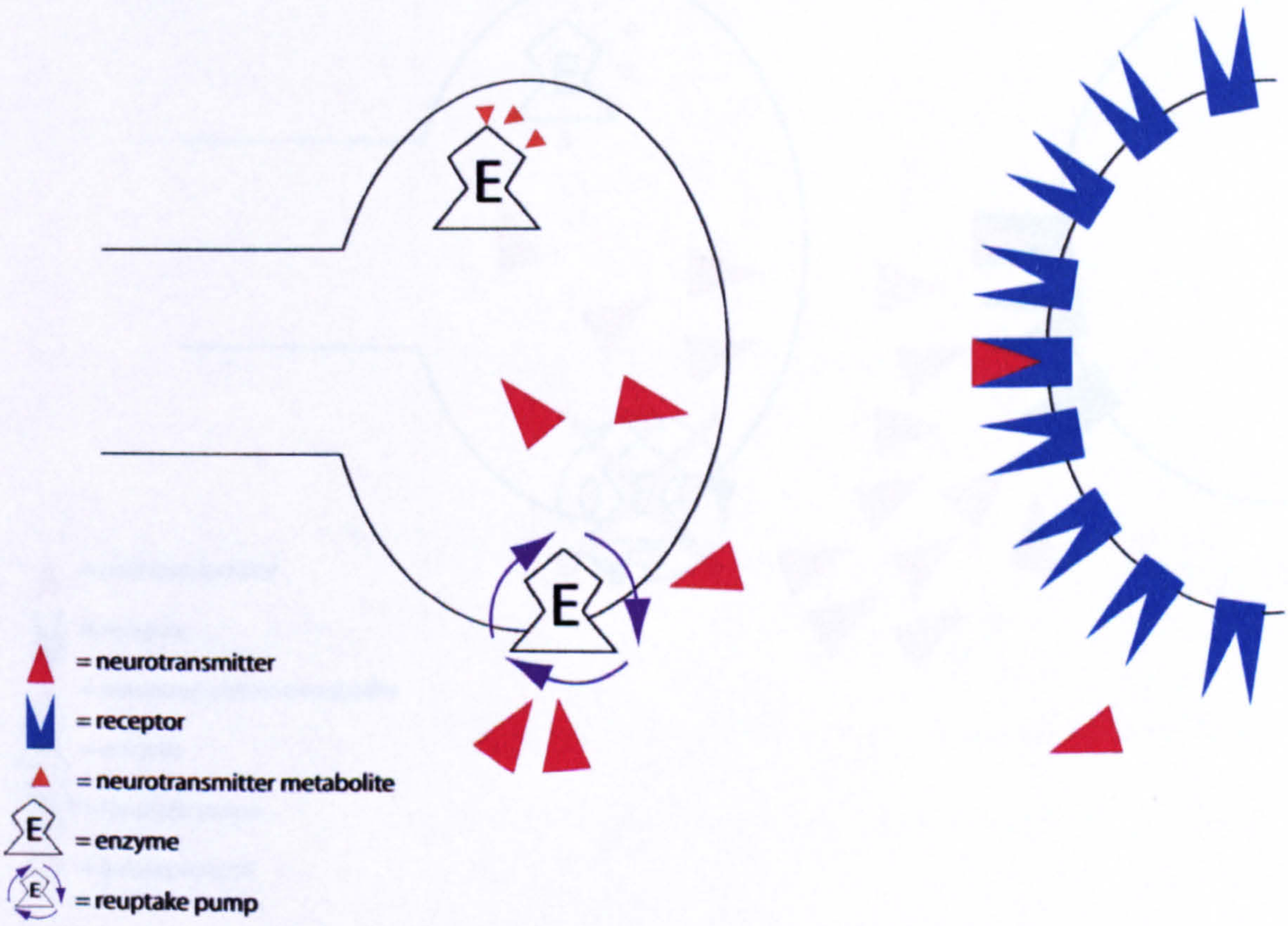


Figure 1.8: Decrease in neurotransmitter in a depressive illness leads to up -regulation of post-synaptic receptors.

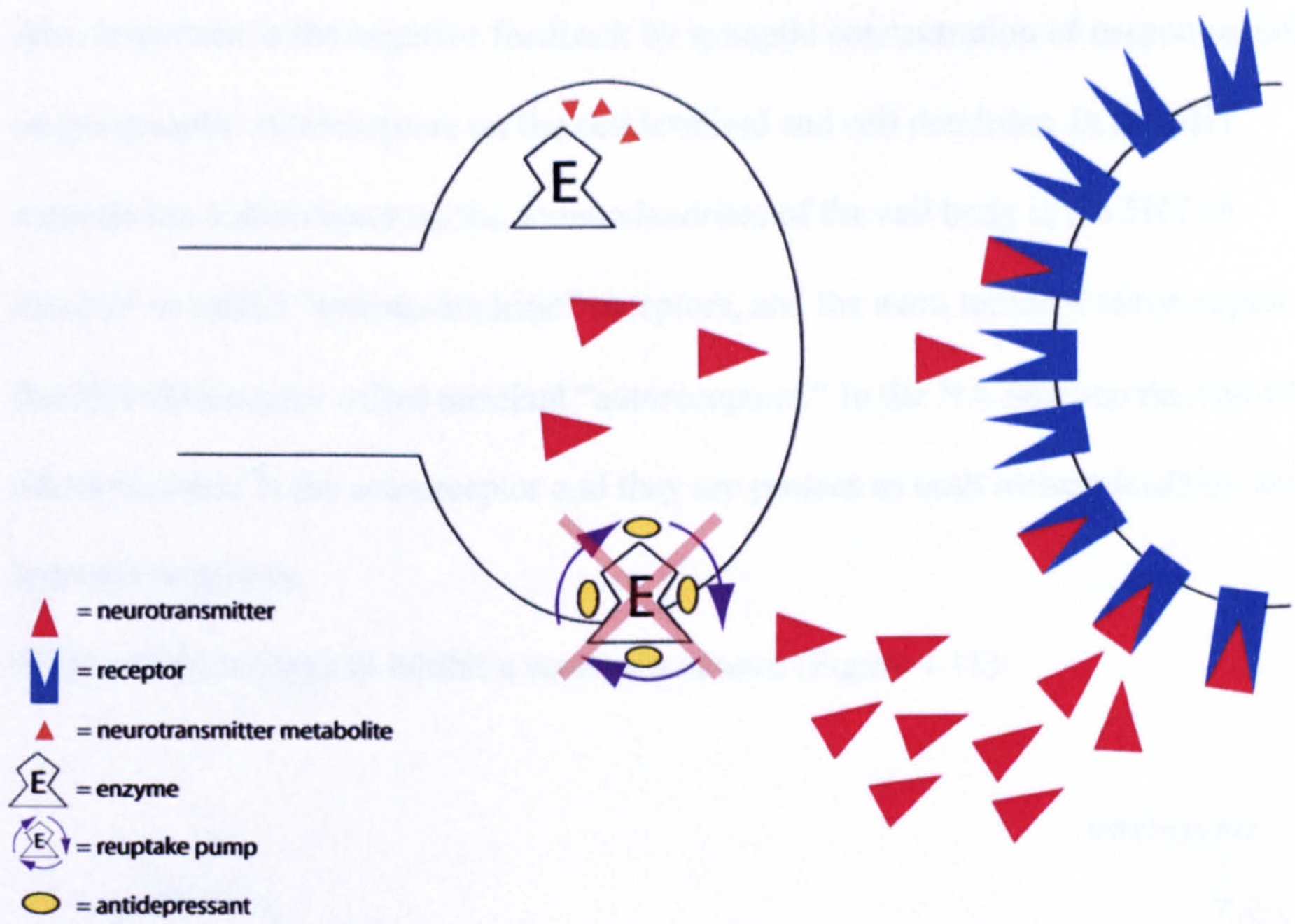


Figure 1.9: Anti-depressant (e.g. an SSRI) blocks re-uptake pump so that there is more neuro-transmitter in the synapse.

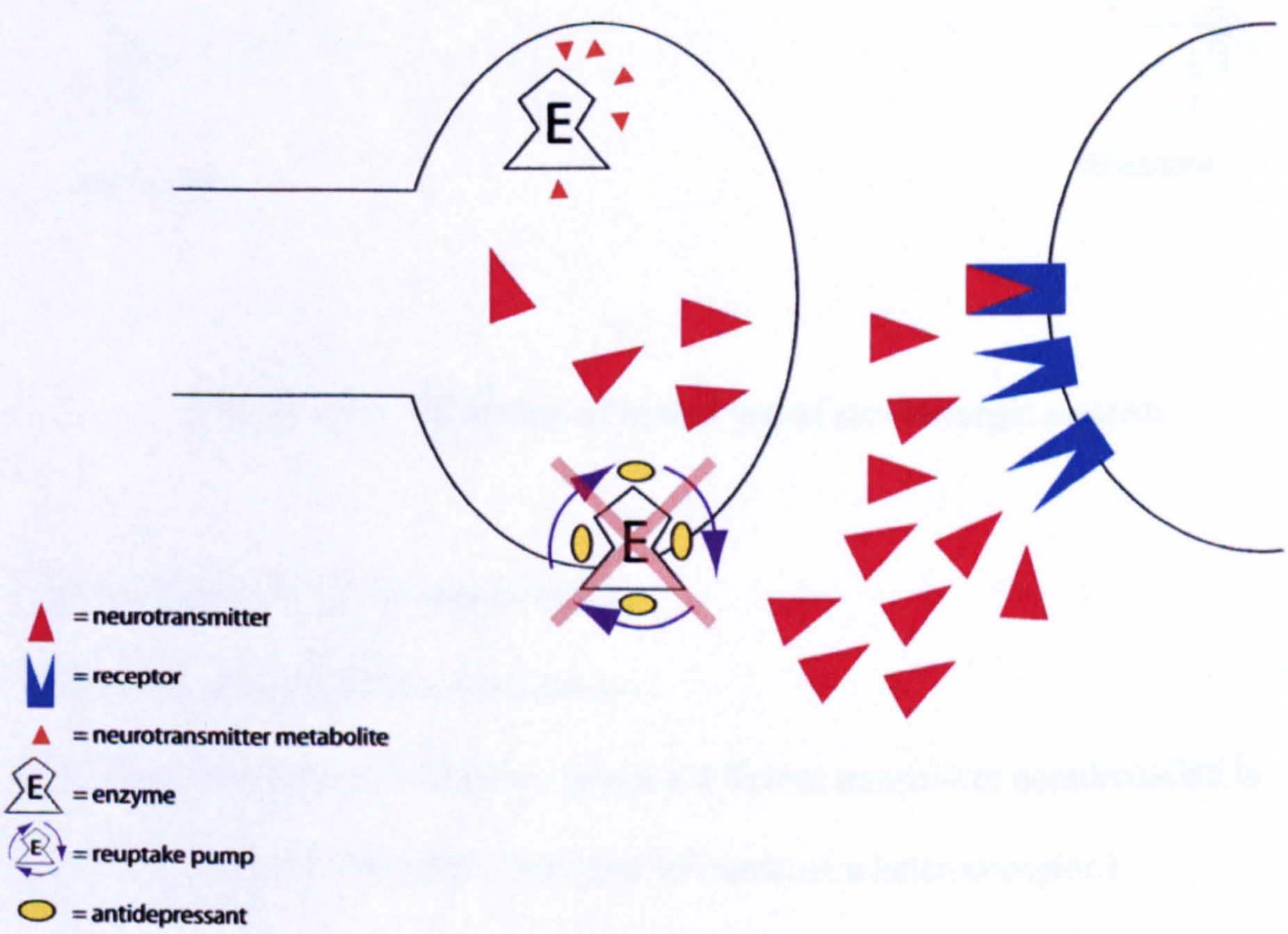


Figure 1.10: Down-regulation of receptors due to increased amount of neuro-transmitter in the synapse

Also important is the negative feedback by synaptic concentration of neurotransmitter on presynaptic autoreceptors on the cell terminal and cell dendrites. In the 5HT neurone the autoreceptor on the somatodendrites of the cell body is the 5HT1A receptor so called "somatodendritic" receptors, and the axon terminal autoreceptor is the 5HT1D receptor called terminal "autoreceptors." In the NA neurone the alpha2 adrenoreceptor is the autoreceptor and they are present as both somatodendritic and terminal receptors.

There are three ways to inhibit a serotonin neuron (Figure 1.11)

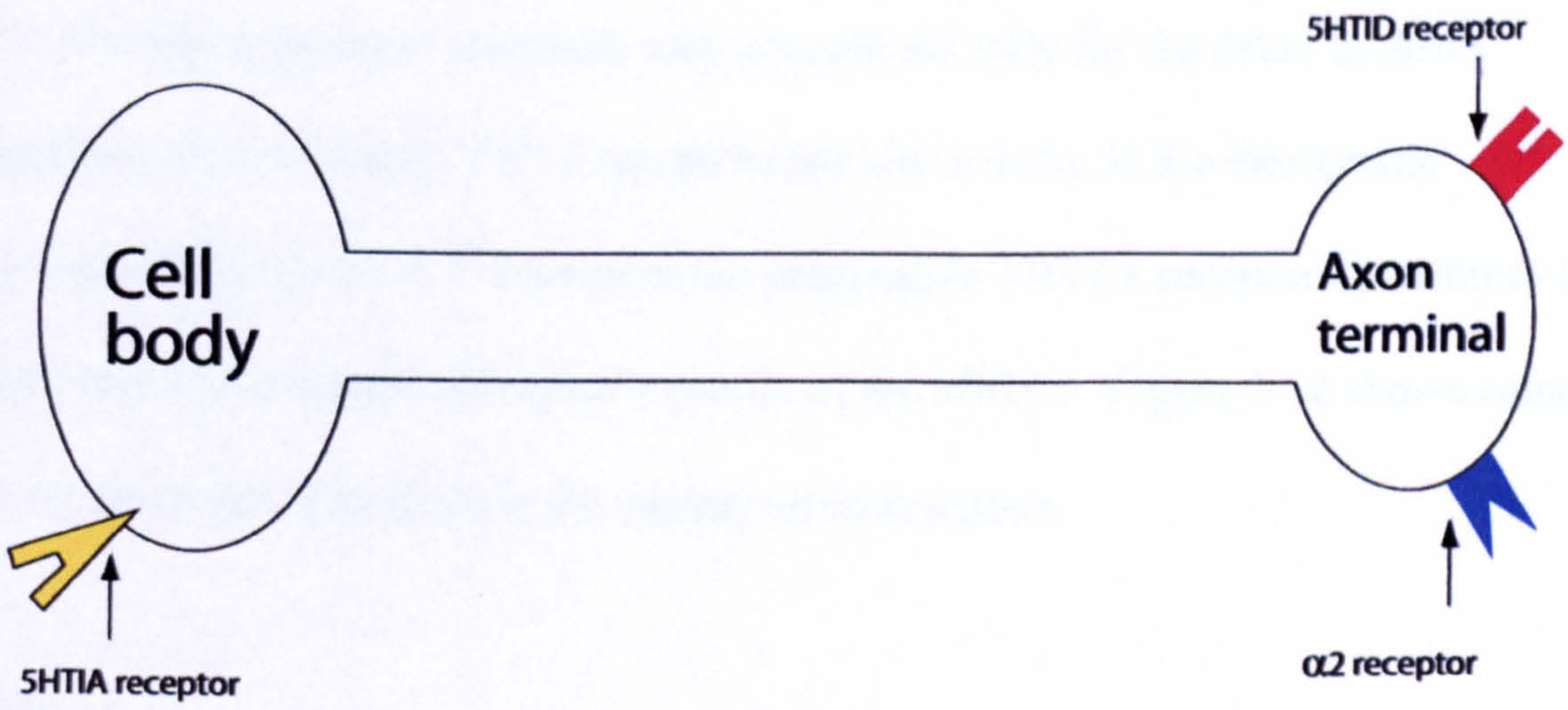


Figure 1.11: Methods of inhibition of serotonergic neuron

1) By stimulating 5HT1A autoreceptors

2) By stimulating 5HT1D autoreceptors

3) By stimulating alpha 2 receptors (since a different transmitter noradrenaline is regulating serotonin, the alpha 2 receptor is known as a heteroreceptor.)

If this feedback mechanism is decreased by a drug that antagonises the autoreceptor, or the autoreceptor is down regulated, (also called disinhibition of the serotonin neuron) there is more neurotransmitter e.g. serotonin available and thus therapeutic effects in depression.

There is however a delay in how soon the increased somatodendritic 5HT (e.g. in the cell body area of the midbrain raphe due to blockade of the 5HT reuptake pump by a SSRI,) can down regulate the somatodendritic autoreceptors in order for the neuron to increase 5HT in axon terminals and to increase its neuronal impulses. The delay in 5HT arriving at the axon terminals may account not only for the delay in down regulation of postsynaptic 5HT2 receptors but also a delay in the therapeutic consequences of SSRI'S.[26] Therefore the presynaptic 5HT1A receptor contributes in a major way to the overall therapeutic profile of the SSRI's. Figure 1.12 shows some of the key serotonin pathways in the central nervous system.

5HT2

A very important postsynaptic regulatory receptor is the 5HT2 receptor. However 5HT2 receptor stimulation as well as playing a role in some of the therapeutic effects of SSRI's, can mediate several of the side effects of SSRI'S (Table 1.5.) Also stimulation of the 5HT3 receptor appears to be responsible for some of the gastrointestinal side effects of the SSRI's. These effects are mediated in the CNS and gut.

Type of receptor	Receptors stimulation effects
5HT1A presynaptic	Antidepressant
	Anti panic
	Anti OCD
	Anti bulimia
5HT1A postynaptic	Decrease Temperature
5HT1D presynaptic	Anti migraine
5HT2A postsynaptic	Antidepressant
	Increase Anxiety
	Increase Temperature
	Decrease sexual functioning
	Decrease sleep
	Anti OCD
	Anti bulimic
	Increase Hallucinations/Psychosis
5HT3 postsynaptic	Nausea
	Decrease Appetite
	Increased Gastrointestinal activity

Table 1.5: Summarising the main effects of stimulation of 5HT receptors

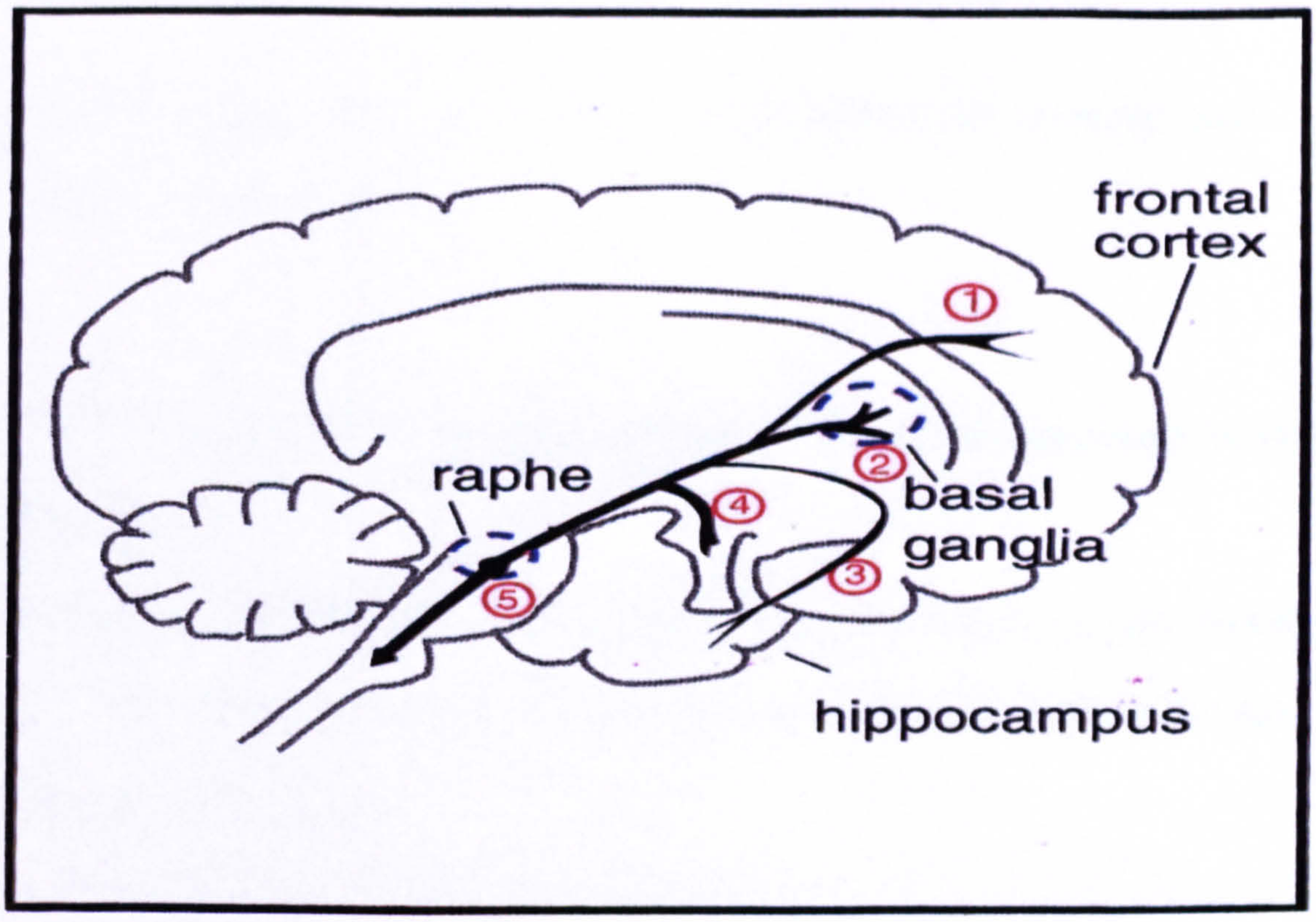


Figure 1.12: Key serotonin pathways in the CNS.

When the serotonin neurone is disinhibited it turns on serotonin release in several pathways simultaneously. The areas in the brain in which some therapeutic effects are thought to be mediated are as follows:

Pathway 1: Depression: disinhibition of the pathway from midbrain raphe to frontal cortex.

Pathway 2: OCD: disinhibition of the pathway from midbrain raphe to basal ganglia.

Pathway 3: Panic Disorder: disinhibition of the pathway midbrain raphe to limbic cortex and hippocampus.

Pathway 4: Bulimia: disinhibition of the pathway midbrain raphe to hypothalamus.

Pathway 5: From midbrain raphe descending down the spinal cord.

A summary of antidepressant blockade and receptor effects with measured uptake blockade is shown in Table 1.6.

Explanation of some of the more common side effects of antidepressants by their receptor action

Side effects of TCAs include orthostatic hypotension, dizziness, dry mouth, blurred vision, urinary retention, constipation and weight gain. These are due to their other receptor actions (Table 1.6).

Serotonin specific reuptake inhibitors (SSRIs) are safer in overdose than the TCAs. They do, however, cause agitation, akathisia and sexual dysfunction.

Trazodone and nefazodone are also known as the SARIs (serotonin antagonist and reuptake blockers). They block 5HT reuptake weakly but powerfully block the postsynaptic 5HT2 receptor. Trazodone, also a 5HT2 antagonist, blocks histamine receptors powerfully and is therefore sedating. Trazodone administration together with an SSRI can be useful to mitigate the sleep disruptive effects of the SSRIs. Trazodone also blocks cholinergic receptors. A rare side effect is priapism due to its alpha antagonist blocking properties. Nefazodone is a less sedating as it is less histaminergic than trazodone but it also weakly blocks noradrenaline uptake which may offset its alpha-one adrenergic blocking properties therefore accounting for less association with orthostatic hypotension and priapism.

The stimulation of 5HT receptors by SSRIs may treat depression but the stimulation of 5HT receptors elsewhere in the body may cause side effects e.g. 5HT in the forebrain can cause agitation and excitement and in the spinal cord lead to sexual dysfunction. However the SARIs e.g. nefazodone and trazodone, which combine 5HT reuptake blockade with stronger 5HT2 antagonism use both these actions to contribute to their therapeutic effect and reduce the undesired actions of 5HT. Clinically important consequences of blocking 5HT2 receptors are: decreased anxiety, enhanced SWS, less sexual dysfunction and sedation.

Nefazodone does not usually produce the unwanted side effects of SSRIs, but some may occur due to excessive blocking of 5HT2 receptors. For example, over-sedation, palinopsia (visual streaking) and asthenia can occur. Other side effects of nefazodone are due to the metabolite mCPP, which is a 5HT2A/2C agonist. 4 % of Caucasians lack the enzyme cytochrome P450 2D6 which is also inhibited by SSRIs. If 2D6 is absent or inhibited lots of mCPP can form leading to stimulation rather than blockade of 5HT2A/2C receptors causing dizziness, light headedness, insomnia, agitation and nausea. i.e. opposite effects to the parent compound nefazodone itself. Nefazadone also inhibits cytochrome P450 enzyme 3A3,4 and care should be taken if it is prescribed with potentially toxic substrates of 3A3,4 e.g. terfenadine. However, as will be discussed later, nefazodone can be a useful hypnotic antidepressant.

Figures 1.13 to 1.18 depict the major classes of antidepressant.

Antidepressant		Uptake blockade (Ki)			Receptor effects					
		NA	5HT	DA	ACh	H_1	α1	α_2	$5HT_{1A}$	5HT 2
SSRIs	fluoxetine	+	+++ +							
	citalopram		+++							
	fluvoxamine		+++							
	paroxetine	++	+++ +	+	✓					
	sertraline	+	+++ +	++						
SNRI	venlafaxine	++	+++							
NARI	reboxetine	++	+							
TCAs	clomipramine	++	+++ +		✓	✓	✓			
	imipramine	++	+++		✓	✓	✓			
	desipramine	+++ +	++		✓	✓				
	amitriptyline	++	+++		✓	✓	✓			✓
	dothiepin	++	+++		✓	✓	✓			
	lofepramine	+++	++		✓		✓			
	trimipramine		+		✓	✓	✓			✓
Other	mianserin	++				✓	✓	✓		✓
NaSSA	mirtazapine					✓		✓		✓
SARI	trazodone		+			✓	✓		✓	✓
SARI	nefazodone	+	+	+			✓		✓	✓
NDRI	bupropion	+		+						

KEY: ACh= acetylcholine, DA=dopamine, NA= noradrenaline, NARI= noradrenaline reuptake inhibitor, SER=serotonin, SNRI= selective noradrenaline reuptake inhibitor, SSRI=selective serotonin reuputake inhibitor,
TCA=tricyclic anitdepressant
NaSSA= Noradrenergic and Specific Serotonergic Antidepressant
SARI = Serotonin Antagonist and reuptake inhibitor
NDRI= Noradrenaline and Dopamine reuptake inhibitor
Ki represents transporter binding affinity; ✓= Ki < 100 nmol/L, + indicates 100-1000 nmol/L, ++ indicates 10-100 nmol/L, +++ indicates1-10 nmol/L, ++++ indicates <1 nmol/L

Table 1.6: Properties of antidepressants (adapted from Wilson and Argyropoulos 2005 with kind permission)[27]

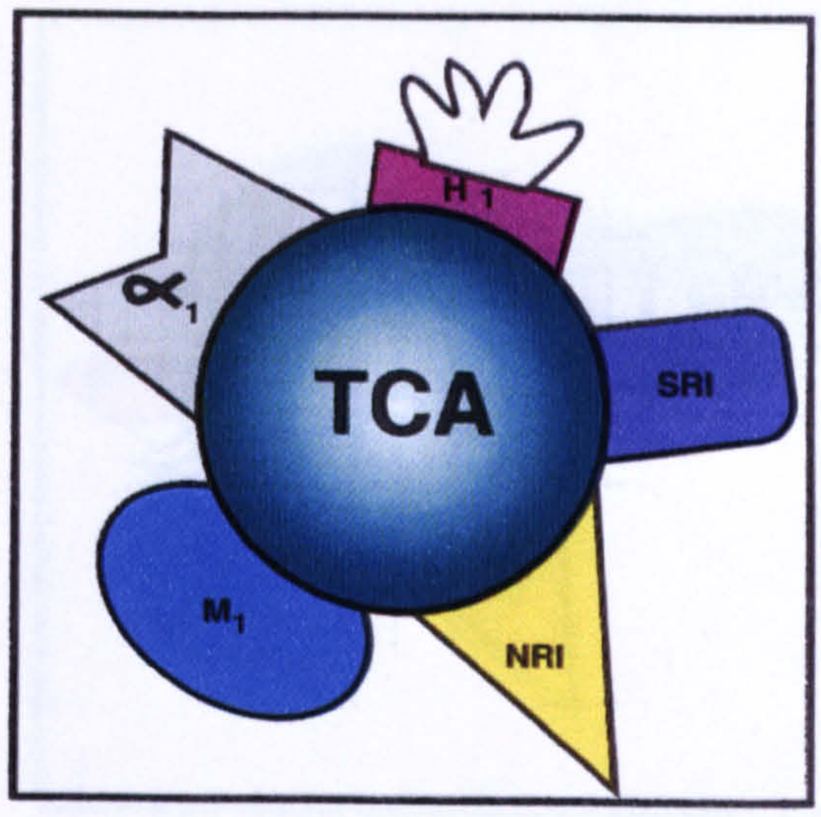


Figure 1.13: **A diagram of a tricyclic antidepressant. TCAs have 5 main actions: (i) serotonin re-uptake inhibition (SRI); (ii) noradrenaline re-uptake inhibition (NRI); (iii) anticholinergic-antimuscarinic action (M1); (iv) alpha-1 adrenergic antagonism (α1); and (v) anti-histaminergic action (H1).**

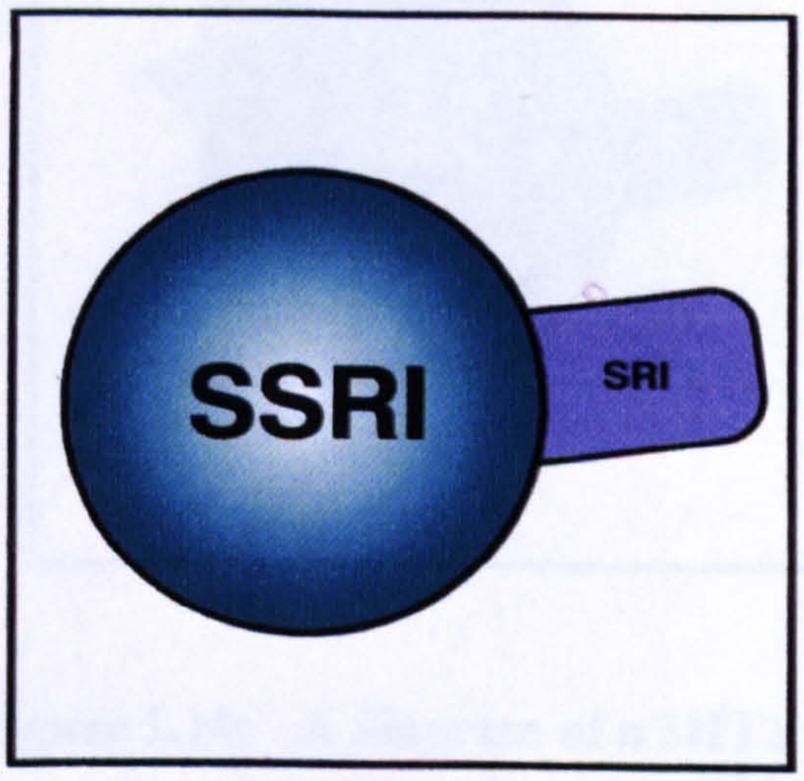


Figure 1.14: **A diagram of a selective serotonin re-uptake inhibitor. Four of the five main pharmacological actions of TCAs have been removed and only serotonin reuptake inhibition remains (SRI) – hence the name *selective* serotonin reuptake inhibitor.**

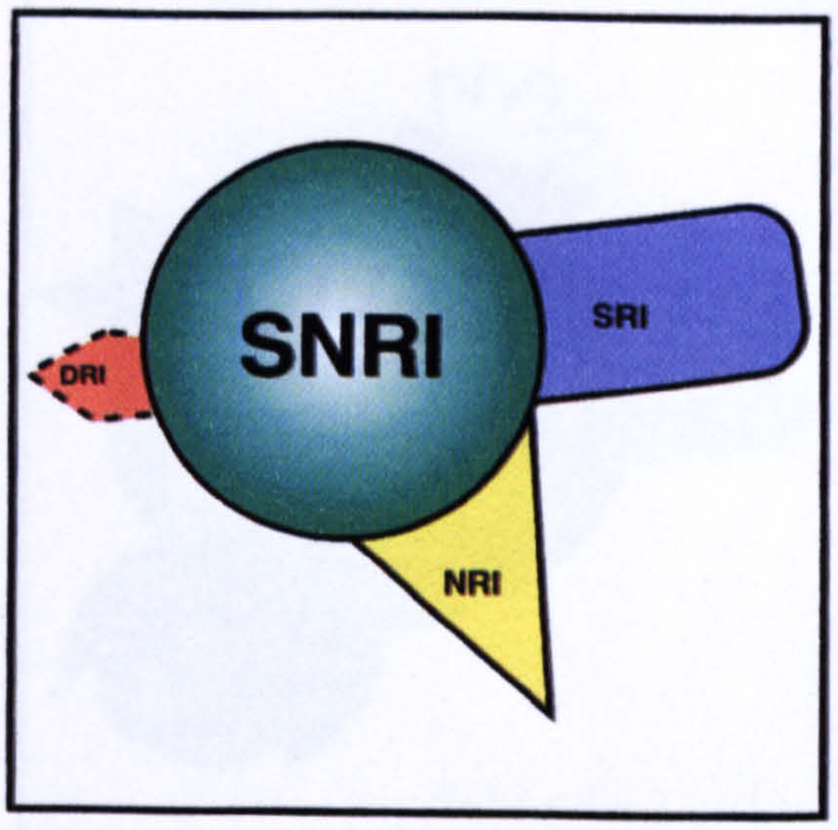


Figure 1.15: **A diagram of a dual re-uptake inhibitor (e.g. venlafaxine) which combines the actions of both a serotonin re-uptake inhibitor (SRI) and a noradrenaline re-uptake inhibitor (NRI). At high doses there is also some moderate dopamine re-uptake blockade (DRI).**

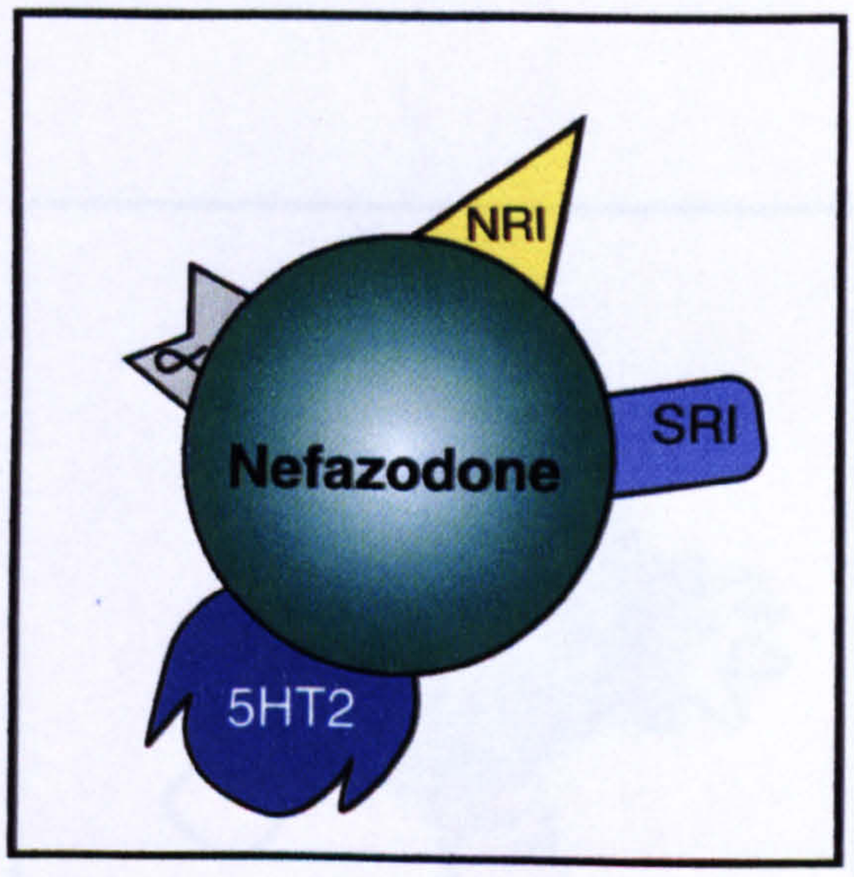


Figure 1.16: **A diagram of a 5HT2 antagonist (e.g. Nefazodone). 5HT2 antagonists have additional and varied pharmacological properties which help distinguish one from another. Nefazodone, for example, couples 5HT2 receptor blockade with serotonin re-uptake inhibition.**

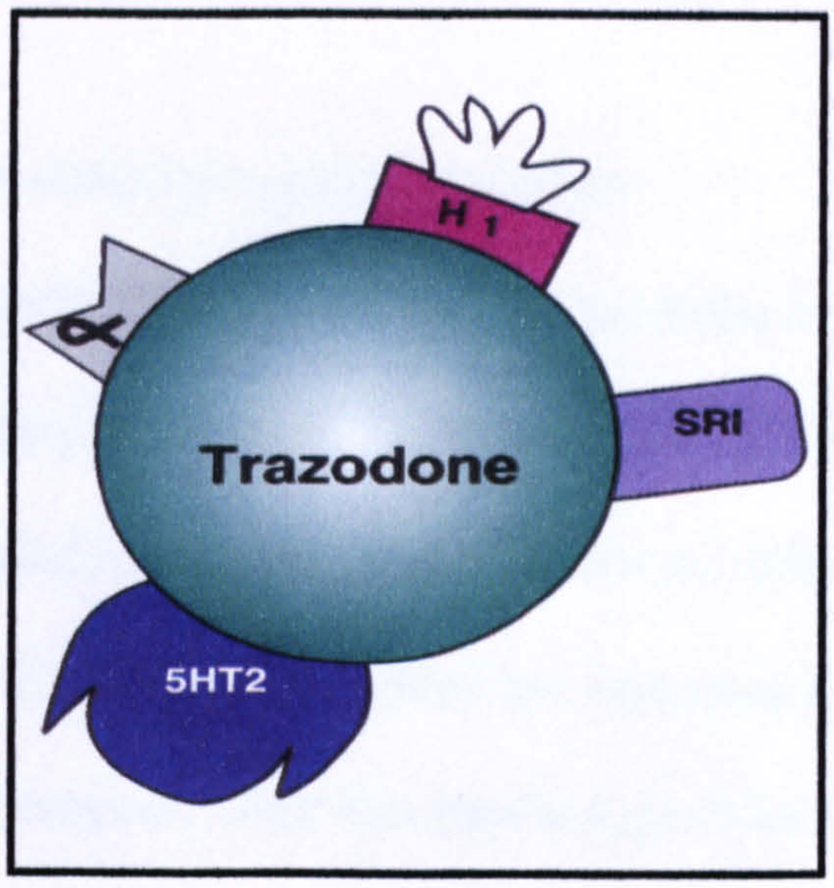


Figure 1.17: Trazodone blocks histamine receptors but is not a noradrenaline antagonist.

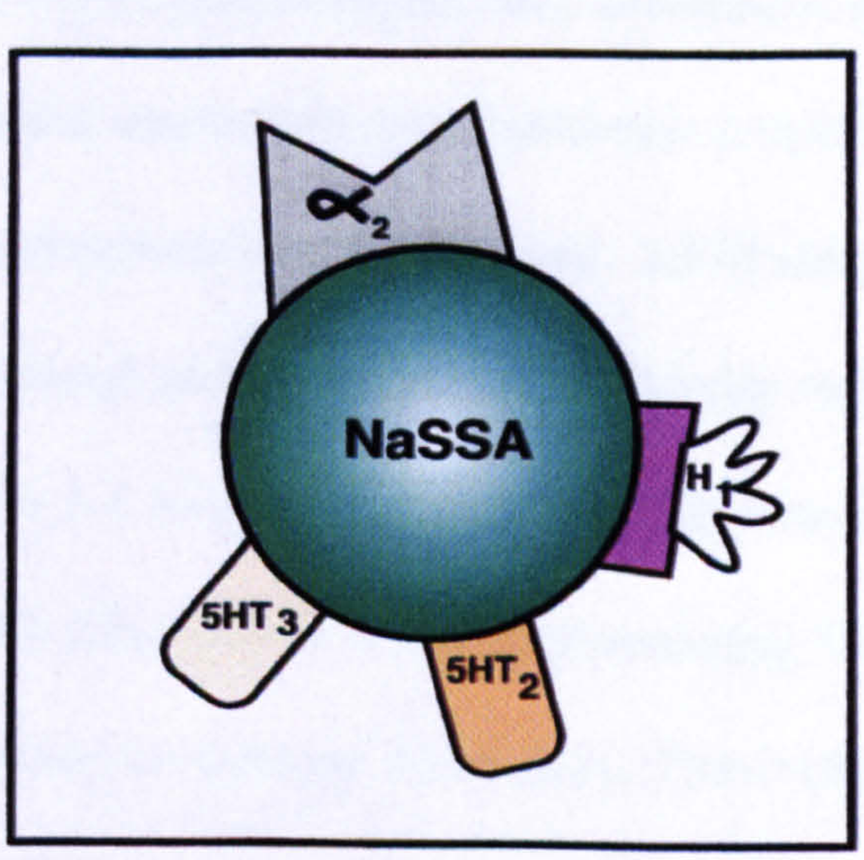


Figure 1.18: A diagram of a noradrenergic and specific serotonergic antidepressant (NaSSA) e.g. Mirtazapine.

1.8 Antidepressants and sleep

Most antidepressants alter sleep in the opposite direction to depression related changes, (This also occurs with ECT). This may mean that sleep is an indirect biological marker of the therapeutic effects of antidepressants. Patients who have sleep changes when they are depressed may respond better to pharmacological treatments rather than psychological treatments.[28]

The majority of antidepressants suppress REM sleep and increase REM latency.[27] TCA treatment is also associated with increased REM density. In general, the ability of many antidepressant drugs to decrease REM sleep can be attributed to facilitation of noradrenaline and/or 5HT function or to muscarinic / cholinergic blockade. The potent muscarinic /anticholinergic properties particularly of TCA's mean all three mechanisms may be involved. REM sleep changes occur almost immediately although as mentioned above receptor regulation changes and antidepressant effect take 2-3 weeks to occur. This immediate effect is thought to be due to increases in 5HT from uptake blockade stimulating 5HT1A receptors in the pontine tegmentum that act to suppress REM sleep. The evidence for this is based on the fact that in 5HT1A knockout mice the REM sleep suppressing effect of citalopram is absent,[29] and in humans selective 5HT1A agonist drugs e,g buspirone are REM sleep suppressing.[30] Also, decreasing 5HT availability by rapid tryptophan depletion in patients taking SSRIs has been shown to reverse the SSRI induced REM sleep suppression. This happens almost immediately but changes in 5HT receptor sensitivity to increased levels of 5HT, which modulate antidepressant response in the frontal cortex, takes 2-3 weeks.[30 31]

REM sleep is suppressed early in treatment but tends to return to baseline at about 8 weeks.[32] If SSRIs are stopped REM sleep shows a rebound increase within a week, although ROL is less susceptible to these rebound effects. REM sleep suppression after SSRI treatment is probably caused by the increased levels of synaptic serotonin and mediated through the 5HT1A receptor.

It has been suggested that the improvement in the symptoms of depression is related to REM sleep suppression,[33] however not all antidepressants act by suppressing REM sleep e.g. nefazodone, and trimipramine.

The commonly prescribed antidepressants effects on sleep are summarised in Table 1.7.

Drug	Patient group	Acute (1-2 nights) decrease in REM	Acute (1-2 nights) increase in ROL	Acute (1-2 nights) sleep continuity	Subchronic (5-10 nights) decrease in REM	Subchronic (5-10 nights) increase in ROL	Subchronic (5-10 nights) sleep continuity	Chronic >21 nights decrease in REM	Chronic >21 nights increase in ROL	Chronic >21 nights sleep continuity	Withdrawal rebound of REM
SSRI fluoxetine	HV	✓/–	✓/–	↓	✓	✓	↓	✓	✓✓	↓	✓
	Dep				✓✓	✓	↓	✓	✓	↓	
SSRI citalopram	HV	✓✓	✓✓	↓	✓✓	✓✓✓	↓	✓✓	✓✓	↓/–	✓
fluvoxamine, paroxetine, sertraline	Dep	✓✓	✓✓	↓	✓✓	✓✓✓	–	✓✓	✓✓	–	✓
SNRI venlafaxine	HV	✓✓	✓✓	↓							
	Dep										
NARI reboxetine	HV										
		–	–	↓	✓	✓	–	✓	✓	–	
TCA (eg imipramine, clomipramine)	HV	✓✓	✓✓	↓	✓✓	✓✓✓	↓	✓✓		↓	✓
	Dep	✓✓✓	✓✓✓	↓	✓✓	✓✓✓	–	✓	✓✓	– (CLOM↓)	
TCA (eg amitriptyline, dothiepin)	HV	–	✓✓	↑	✓	–	–	✓	✓	–	✓
	Dep	✓	✓✓	–	✓✓	✓✓	–	✓	✓✓	↑	✓
lofepramine	HV	✓✓	✓	–	✓✓	✓	↓				
	Dep										
trimipramine	HV	✓	–	↑			↑		✓		
	Dep	–	–	↑	–	–	↑	–	–	↑	
MAOI phenelzine	HV				✓						
	Dep	–	–		✓✓✓	✓✓✓		✓✓✓	✓✓✓		✓
moclobemide	HV	✓	–	↓							
	Dep	–/↑	✓	–	–	✓	↑	–	✓	–	✓
mianserin	HV	✓	✓	↑	✓	–	–				
	Dep	✓	✓	↑				✓	✓	↑	
mirtazapine	HV	–	✓	↑							
	Dep	–	–	↑	–	–	↑	–	–/✓	↑	
nefazodone	HV	–	–	–	–	–	↑				
	Dep	–	–/↓	↑	–	–	↑	–	–/↓	↑	
trazodone	HV	–/✓	–/✓	–	✓		↑				✓
	Dep	–	–	↑	✓	✓	–/↑	–	✓	↑	
bupropion	HV										
	D	–	–	–				–/↓	✓/–	–	

Table 1.7: **Sleep Effects of Antidepressants (adapted from Wilson and Argyropoulos 2005 with kind permission)**[27]
Significant findings compared with baseline, depressed patients (Dep) or placebo, healthy volunteer (HV) studies
Shaded fields – no results reported, dashes – no significant difference.
REM decrease = ✓10-30%, ✓✓ 30-60%, ✓✓✓ >60%, REM onset latency (ROL) increase = ✓ 30-100%, ✓✓ 100-200%, ✓✓✓ >200%
sleep continuity = ↑improved, ↓ worsened

Tricyclics (TCAs)

TCAs are potent REM sleep suppressors. Cloimpramine and imipramine are the most potent. They increase REM latency and decrease total REM sleep time with maximal effects after only a few days. The TCAs differ from each other in their effects on sleep onset and maintenance, in healthy volunteers and depressed patients. Cloimipramine, imipramine, dothiepin, and lofepramine tend to decreases sleep continuity, although amitryptiline may increase it (Table 1.7). Amitryptiline also stimulates the 5HT2 receptor as do the sleep promoting antidepressants e.g. nefazodone and mirtazepine. (The anti-psychotics that are sleep promoting are also 5HT2 antagonists e.g. olanzapine.[34]) Trimipramine is the only TCA that is robustly sleep promoting with decreased SOL's, increased TST's and higher sleep efficiencies in short term studies of healthy volunteers and depressed patients. It does not suppress REM sleep and it is only a weak monoamine reuptake inhibitor. Trimipramine's effects may be sustained in long term treatment of depression and insomnia.

In summary polysomnographic studies of the TCAs generally support the clinical practice of using sedating TCAs for depressed patients with insomnia and the use of more activating TCAs for the hypersomnolent depressed group.

Monoamine Oxidase Inhibitors (MAOIs)

These are the most potent REM suppressors e.g. phenelzine and they can suppress REM sleep completely.[35] The effects are delayed compared to TCAs, maximal after about a week, and are associated with a large REM rebound on withdrawal 10 days after stopping the drug.

Reversible MAOI A inhibitors, (RIMAs) e.g. moclobemide may only be mild REM sleep suppressors.[36]

Selective Serotonin Reuptake Inhibitors (SSRIs).

SSRIs cause potent REM sleep suppression and increased REM latency

Fluoxetine

Studies have shown a substantial increase in REM latency compared to baseline in normal volunteers and depressed patients.[32 37] These studies have also shown fluoxetine can decrease REM sleep time by 3-5%, increase stage 1 sleep and increase awakenings during sleep.

Paroxetine

Sharpley[38] (1996) compared effects of paroxetine, 20mg/day titrated up to 30mg/day on day 4, with nefazodone 100mg bd increased to 200mg twice a day on day 4 and placebo in 37 healthy volunteers. Compared to placebo subjects receiving paroxetine showed decreased TST, decreased sleep efficiency and an increase in wakefulness after sleep onset (WAS0). REM sleep amount was significantly reduced and REM latency increased at day 1, 6 and 16 in the paroxetine group.

SSRIs cause similar changes in sleep onset and maintenance in healthy volunteers and depressed patients. They increase stage 1 sleep, increase arousals and WASO.[32 37] Most studies show this effect but it tends to decrease after a few days except in the case of fluoxetine that may disrupt sleep continuity for up to 8 weeks.[37] SSRIs may increase wakefulness at least initially because of their activation of 5HT2A/C receptors.

Mirtazapine

Mirtazapine is a potent 5HT2 and 5HT3 antagonist. It has clinically important consequences as it stimulates 5HT1A receptors while blocking 5HT2 and 5HT3 receptors. It also blocks the alpha2 autoreceptor, leading to increased 5HT and NA. 5HT2 and 5HT 3 effects may account for its antidepressant effect but it is also anxiolytic and sedating. There tend to be less problems with sexual dysfunction and nausea. It is a potent histamine blocker and it may increase sleep continuity due to this action. Weight gain is its main side effect probably related to its histamine stimulation. It increases ROL only modestly.[39]

Trazodone and Nefazodone

Trazodone, in normal subjects, decreases numbers of awakenings and arousals, increases SWS increases REM latency and decreases REM sleep time, however results have been variable and only small numbers studied.[40] The most consistent effect on sleep in depressed patients is REM suppression, either decreased REM time or increased REM latency[41].

Nefazodone, a phenylpiperazine, (with active metabolites hydroxynefazodone and mCPP) may be unique in that it does not appear to suppress REM sleep in either healthy controls or in depressed patients. In two studies in normal volunteers it has caused an increase in REM sleep[40 42] and in one study, see below, in depressed patients compared to fluoxetine.[37] It also exerts minimal effects on sleep continuity by either decreasing awake and movement time and decreasing number of awakenings or by not affecting these parameters.

Nefazodone and fluoxetine sleep effects and antidepressant efficacy have been compared in a multicentred trial in 125 patients with major depression.[37] Clinical efficacy was comparable for both groups. With respect to sleep parameters patients receiving nefazodone demonstrated increased sleep efficiency, while patients on fluoxetine demonstrated a significant decrease in sleep efficiency and a significant increase in number of awakenings compared to baseline scores. Patients taking nefazodone demonstrated a total increase in total REM sleep time in contrast to the expected REM suppression associated with fluoxetine treatment.

How does nefazodone work to improve depression and promoting sleep? It has been shown to possibly increase REM sleep in healthy volunteers and in depressed patients compared to fluoxetine, as above. Nefazodone has weak antagonist activity at alpha one receptors which could lead to the increase in REM sleep in the reported studies above, but its alpha antagonist receptor properties are weaker than trazodone's which decreases REM sleep. mCPP, nefazodone's metabolite also decreases REM sleep. Nefazodone's weak alpha one antagonist receptor blocking properties may account for its role in improving sleep continuity. Nefazodone's role in decreasing awakenings may be that its 5HT reuptake blocking effects are compensated by its 5HT2A/2C receptor agonist activity.

SSRIs or TCAs have no significant effect on SWS in short or long- term treatment and therefore their clinical effects are unclear.

Antidepressant effects are not restricted to REM or SWS sleep, they also alter sleep initiation and consolidation. Non-REM effects tend to be more varied than REM

changes both acutely and chronically and tend to vary depending on the stage of the illness.[27] The main mechanism behind the sedative effects of TCAs, mianserin and trazodone are their histamine receptor and alpha one receptor blockade but it is possible that 5HT2A/2C receptors are involved.

1.9 Insomnia definitions and epidemiology

When asking a patient what they mean when they say they have insomnia they will mention all or some of the following:

Difficulty falling asleep

Nocturnal awakenings

Early morning wakening (EMW) and difficulty falling back to sleep

Un-refreshing sleep

Daytime fatigue

Insomnia has been known and discussed by the scientific community for at least two thousand years beginning with Aristotle's monograph on sleeplessness written in 350 BC. However there is still no overall agreement by patients, healthcare professionals and sleep researchers what constitutes insomnia. The term insomnia is used in a confusing way to describe a disease, complaint, symptom and a finding.

To further complicate matters there are three main classifications of the diagnosis of insomnia. These are:

International Classification of Diseases ICD-10 (WHO, 1992[43])

International Classification of Sleep Disorders ICSD (ASDA 2005[44])

Diagnostic and Statistical Manual of Mental Disorders 4TH edition[45]

The different classification systems are used by different bodies and there are difficulties matching one classification to another which leaves gaps when transferring between the systems.

ICD 10 defines non-organic insomnia as a difficulty falling asleep or maintaining sleep or poor quality sleep at least three times a week for at least a month. DSM-1V (R) gives as the first criterion for insomnia that the predominant complaint is difficulty initiating or maintaining sleep or non-restorative sleep for at least one month.

The International classification of sleep disorders ICSD is the gold standard for sleep researchers and defines insomnia as difficulty in initiating or maintaining sleep. Table 1.8 shows the different classifications of insomnia comparing ICSD, ICD-10 and DSM1V (R).

"Psychophysiological insomnia" is an important cause of insomnia in middle aged women. They are usually previous light sleepers, presenting with a relatively long history of insomnia that waxes and wanes in severity which may have been precipitated by a bout of depressive illness. Sometimes, insomnia has developed gradually "feeding on itself". A hallmark of psychophysiological insomnia is the focused absorption of the patients on their sleep problem while the same patients often minimize other mental or emotional concerns.

It is defined as "a disorder of somatized tension and learned sleep-preventing associations that results in a complaint of insomnia and associated decreased functioning during wakefulness". About 15% of insomniacs seen in sleep disorder clinics have psychophysiological insomnia but the true incidence in the general population is unknown.[44] Primary insomnia is a diagnosis of exclusion and accounts for approximately 30 % of chronic insomnia.

ICSD	ICD-10	DSM 1V R
Adjustment sleep disorder	Non organic insomnia	
Psychophysiological insomnia	Non organic insomnia	Primary insomnia
	Disorder of initiating and maintaining sleep	
Central sleep apnoea syndrome Central alveolar hypoventilation syndrome	Sleep apnoea	Breathing related sleep disorder
Altitude insomnia	Other effects of high altitude	
Short sleeper		
Fatal familial insomnia	Other degenerative diseases	
Idiopathic	Disorder of initiating and maintaining sleep	Primary insomnia
Sleep misperception		

Table 1.8: Different classifications of insomnia, comparing ICSD, ICD-10 and DSM IV R

Prevalence of insomnia

The prevalence of insomnia, as explained above, will depend on how insomnia is defined. Most population prevalence has been obtained through questionnaire and interview surveys inquiring about 'difficulty sleeping' without regard to clinical significance or causal factors. In a review of 25 years of epidemiological studies from 1976-1996 [46],'sleep disorders' in general were reported in 13%- 49% of respondents but "insomnia" specifically was reported in 3%-19% of subjects. Ohayon 2002[47], reviewed the epidemiology of insomnia by dividing the estimates of the prevalence of insomnia into four definitions; insomnia symptoms, insomnia symptoms with daytime consequences, sleep dissatisfaction and insomnia diagnoses. The first definition based on insomnia criteria including report of difficulty initiating or maintaining sleep or non restorative sleep regardless of duration or consequences, recognizes that about one third of a general population presents at least one of them. When daytime consequences are taken into account the prevalence is between 9%-15%. The third definition represents 8-18% of the general population and the last definition is more precise and corresponds to a decision-making diagnosis setting the prevalence at 6%. (Figure 1.19)

These four definitions of insomnia have higher prevalence rates in women and increase with age. In a multinational European survey, the epidemiology of severe insomnia (at least two sleep complaints on 3 nights a week) and its impact on the quality of life and healthcare consumption was assessed in a survey of the general population of five northern European countries.[48] The prevalence of severe insomnia ranged from 4%-22% and was higher in women than men but was not related to increasing age (although most studies do identify the elderly have an increased

incidence of insomnia). The UK had the highest prevalence of 22% with the highest incidence in the Midlands and North East although in another study in the UK the prevalence was similar to the European study.[49] In all countries insomnia had a negative impact on the quality of life and the degree of impairment was directly related to the severity of insomnia. People with severe insomnia also showed a higher level of healthcare consumption. A 'working prevalence" of the incidence of insomnia is therefore that a third of people will suffer with mild problems sleeping but about ten percent of people suffer with severe insomnia at any one time.

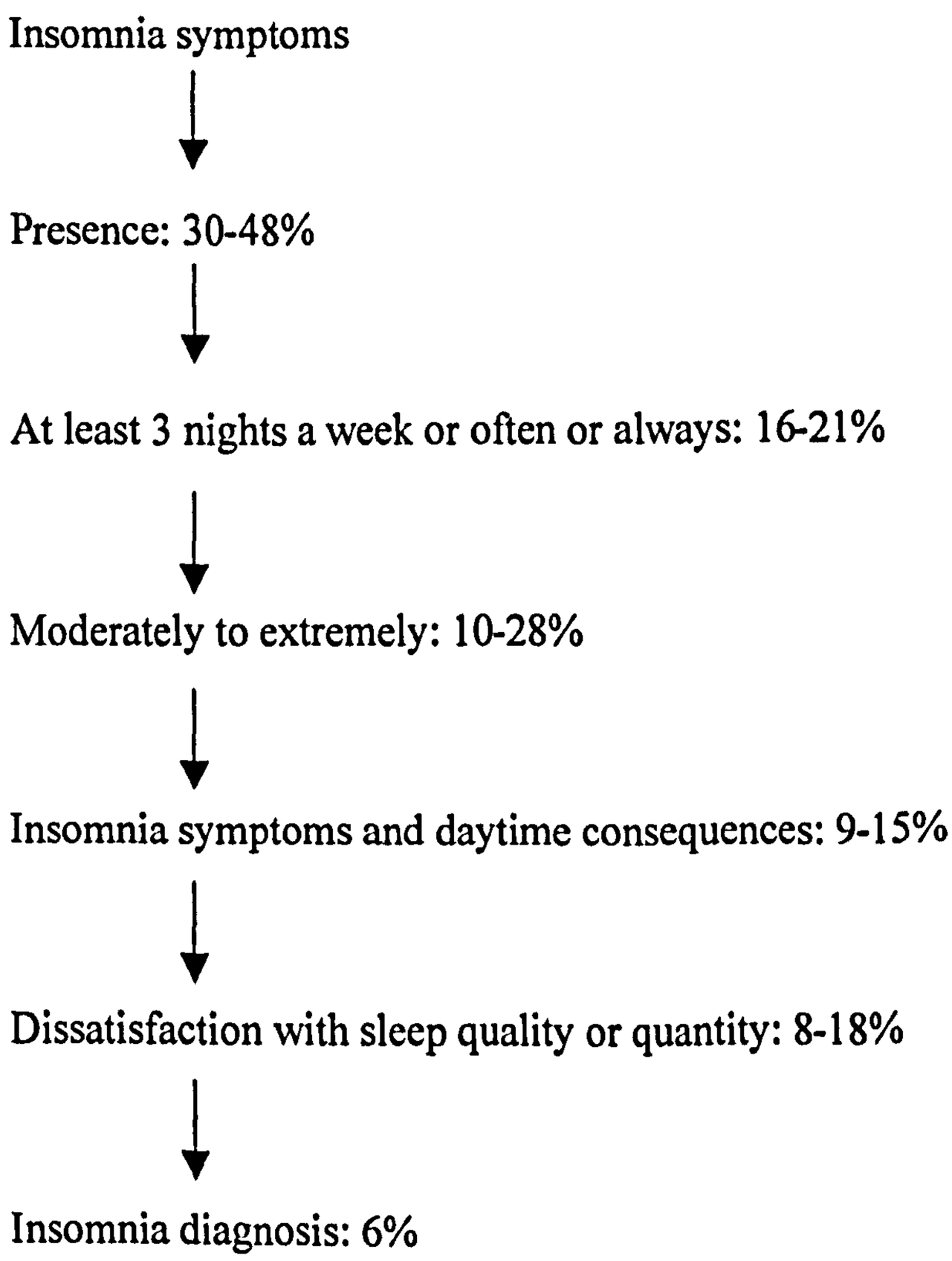


Figure 1.19: Diagnosis of Insomnia

Factors associated with insomnia

Numerous factors are associated with insomnia (Table 1.9.)

	INSOMNIA	
SELF- INDUCED	Life Style	Shift working, irregular sleep wake schedule
	Use, abuse or withdrawal of Psycho-active substances	Alcohol, caffeine, hypnotics, anxiolytics, cocaine, amphetamines, opioid
SECONDARY	Mental disorders	Depressive disorders, bipolar disorders, psychotic disorders, anxiety disorders, eating disorders, psychotic disorders
	Medical Conditions	Arthritis, heart disease, cererbrovascular disease, stomach or gastric ulcer, gastrointestinal disease, obesity, viral or bacterial infection, food or milk allergy, headache, migraine, menopause, head injury, epilepsy, Parkinson's disease, Huntingdon's disease
	Breathing Disorders during sleep	Sleep apnoea, hypoventilation, respiratory insufficiency, sleep related asthma
	Other sleep disorders	Periodic limbs movement disorder Restless leg syndrome Circadian rhythm disorders
PRIMARY	No identifiable factors responsible for the complaint	

Table 1.9: Factors associated with insomnia

1.10 Consequences of insomnia

These include susceptibility to accidents, (including Road Traffic Accidents,) medical and psychiatric morbidity, poor performance at work, absenteeism, and increased mortality.[50] Daytime tiredness and functional impairment in the daytime are also complained of, but there is less clear evidence for a decrease in alertness in laboratory studies of alertness and performance in people suffering from chronic insomnia.[51]

Insomnia sufferers have a higher prevalence of psychiatric disorder and studies of patients in sleep medicine clinics show psychiatric disorder is common.[52] Among a sample of outpatients who were consulting their GP's for insomnia 53% presented with psychiatric symptoms.[53] The risk of depression is probably four times more likely in people with insomnia,[54] and the complaint of insomnia may be an early marker for psychiatric disorders such as depression, anxiety and alcohol abuse. Alcohol abuse and other substance abuse is increased in insomniacs compared to good sleepers. Insomnia can also be associated with many medical conditions.

Chilcott and Shapiro[50](1996) estimated that the direct and indirect costs of insomnia were between 92 -107 billion dollars a year in the U.S.A and Walsh (1995) estimated the direct cost of insomnia to be between 11 billion dollars a year.[55]

1.11 Treatment of insomnia

Potential causes of insomnia (Table 1.7) should be treated. These should be investigated by taking a good history, which includes questions about psychiatric

symptoms and previous medications. It is also important to ask about alcohol use as it is often drunk inappropriately to aid sleep. Sleep diaries may be useful and all patients should be advised about good sleep hygiene.

The role of hypnotic drugs

The duration and cause of the insomnia should be a guide to treatment with medication. If a patient has insomnia secondary to depression then an antidepressant is a useful choice particularly those with sedating properties e.g. mirtazepine or trazodone. Sleep disturbances related to circadian rhythms such as jet lag, shift work, delayed and advanced sleep phase syndrome, should be treated with chronobiotics e.g. melatonin.

The short- term use of hypnotics for the treatment of transient insomnia e.g. due to stress secondary to exams is appropriate. This is usually 2-3 weeks of treatment. It is when addressing the treatment of more chronic insomnia with hypnotic drugs such as benzodiazepines, zopiclone, zolpidem and zaleplon the "Z" drugs that controversy arises.

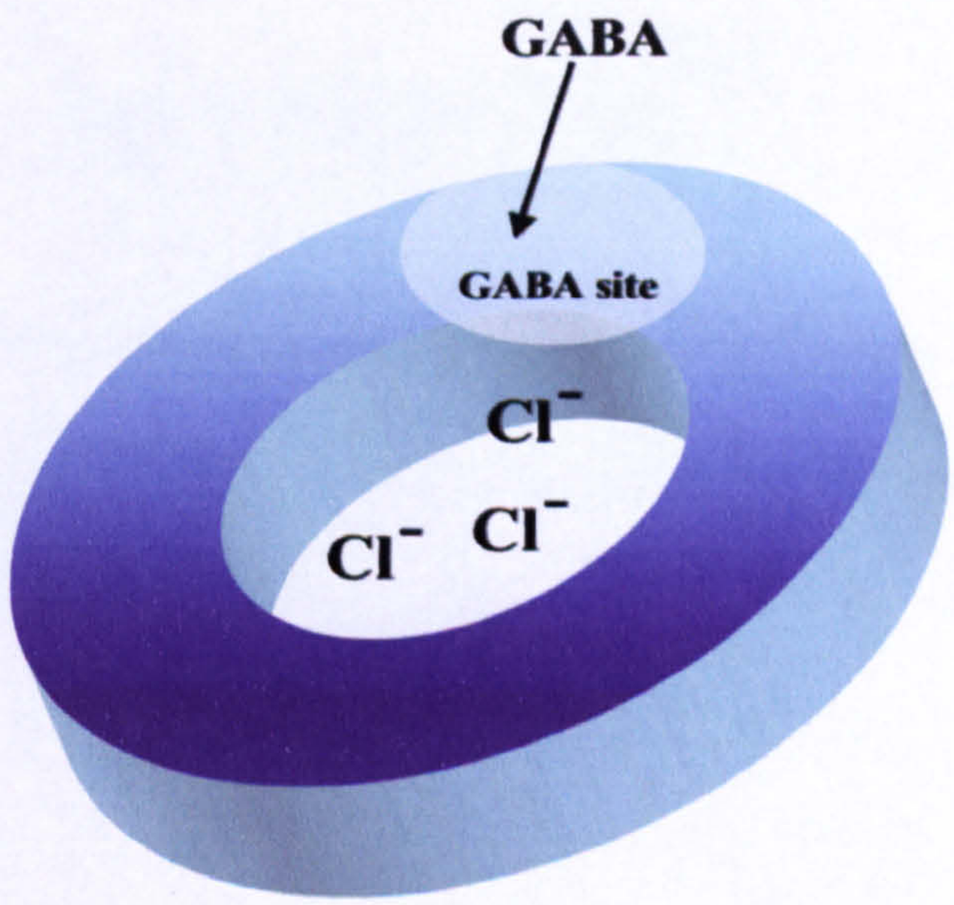
Annual prescription for benzodiazepine hypnotics fell from 10 million to around 6 million in England between 1993 and 2003 and those for the "Z" drugs zopiclone, zolpidem and zaleplon rose from 0.3 million to over 4 million over the same period.[56] This would suggest that prescribers think changing to a Z-drug may avoid the possible problems associated with regular hypnotic use. However, the recent National Institute of Clinical Excellence (NICE) guidelines have recommended that there is no evidence from a meta analysis to suggest that the "Z" drugs should be used in preference to

benzodiazepines in clinical practice due to no difference on outcome measures on insomnia.[57] (This is discussed further later in this chapter.) Table 1.10 shows the pharmacokinetic profiles of the main hypnotic drugs.

1.12 Psychopharmacology of hypnotic drugs

To understand how sedative hypnotic drugs e.g benzodiazepines, zopiclone, zolpidem, zaleplon, barbiturates, and alcohol act in the brain one has to look at the benzodiazepine receptor. These drugs interact with specific binding sites on the GABA A receptor also known as the benzodiazepine receptor. The GABA A receptor is a pentameric protein, comprising of 5 subunits. The principal subunits are alpha, beta and gamma each with many subtypes. They form a rosette around a transmembrane ion channel pore permeable to chloride ions.

Figure 1.20: Diagram of a GABA A Receptor. When GABA binds to the receptor, the chloride channel enlarges, leading to hyperpolarisation of the nerve cell.



Features	Zaleplon	Zolpidem	Zopiclone	Temazepam
Class	Pyrazolopyrimidine	Imidazopyridine	Cyclopyrrolone	Benzodiazepine
Mechanism of Action	Allosteric modulator of GABA. Selective for GABA A Benzodiazepine receptor containing alpha one subunit	Allosteric modulator of GABA. Selective for GABA A Benzodiazepine receptor containing alpha one subunit	Agonist at type GABA A receptor Non selective for subtypes	Agonist at type GABA A receptor
Dose (mg)	5-10	5-10	3.75-7.5	10
Effects on Sleep Architecture	No effect on SWS No effect on REM	No effect on SWS No effect on REM ?delayed first episode	? increases SWS REM decreased	Decreases SWS in high doses Decreases REM
Pharmacokinetic Parameters				
tmax (hrs)	1.4	1.2	3	1.1
t1/2 (hrs)	1	1.9	4.4	9.1
Side Effects				
Most common	Headache	Dizziness, somnolence	Bitter aftertaste, dry mouth	Yes (see text)
Residual effects	No	No	Yes	Yes
Rebound insomnia	No	No	Yes	Yes
Dependence/Abuse potential (increased with history of drug abuse)	Some effect	Some effect	Some effect	
Next day psychomotor or driving impairment	No	Yes	Yes	Yes
Memory impairment	Delayed recall of learnt words	Some effects on anterograde memory	Some effect on word recall	Yes

Table 1.10: Pharmacokinetic profiles of hypnotic drugs

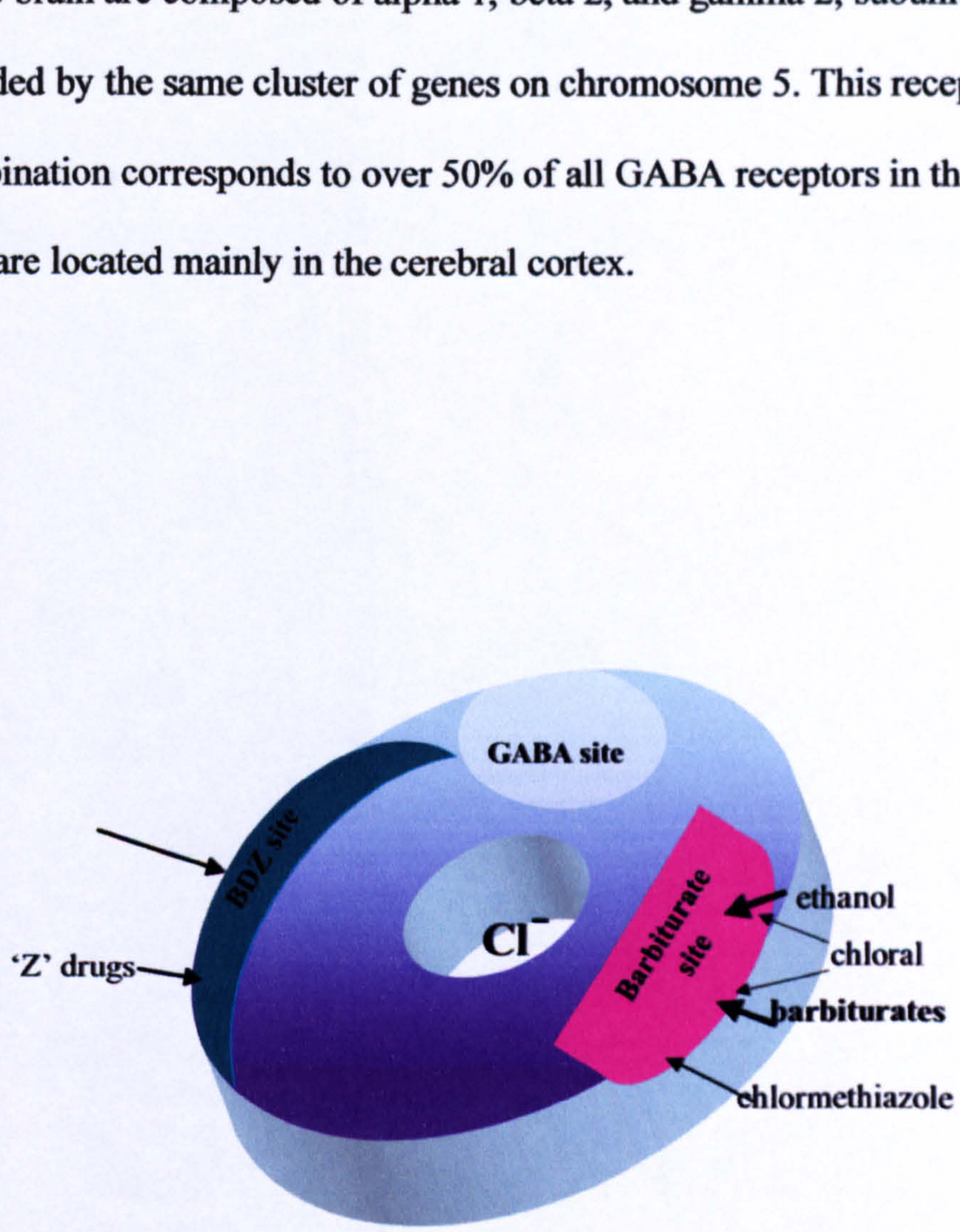
GABA= gamma aminobutyric acid, t1/2 = elimination half-life, tmax = time to reach maximum plasma concentration.

Following occupancy of the beta sub unit by GABA molecules the GABA A receptor columns interact with the chloride channel to open. The increased chloride conductance into the neuron occurs quickly and is inhibitory to the firing neuron. Modern hypnotic drugs like the benzodiazepines, zopiclone (a cyclopyrrolone,), zolpidem (a imidazopyridine), and zaleplon (a pyrazolopyrimidine) bind to the alpha subunit and this is known as the 'hypnotic receptor.' This receptor site allosterically modulates the GABA A site that in turn modulates the chloride channel, causing a large amplification in GABA's ability to increase the conductance of chloride through the channel. These drugs are therefore positive allosteric activators of the GABA A receptor.

This protein is also the target for anxiolytic and anticonvulsant benzodiazepines e.g. alprazolam and clonazepam, benzodiazepine antagonists e.g. flumazenil, and inverse agonists that have the opposite effect to benzodiazepines e.g. psychostimulants and proconvulsants. (Figure 1.21.) Inverse agonists decrease the probability of channel opening in response to GABA and are thus negative allosteric activators of GABA receptors.

There are different forms of the alpha, beta and gamma subunits. It appears that the alpha subunit composition of the receptor determines the benzodiazepine pharmacology of the receptor. Site directed mutagenesis with 'knockout mice" (receptor subunits are deleted due to gene ablation) or "knockin" mice (receptor subunits are mutated in a manner that creates a non-functional receptor site,) has indicated that benzodiazepines bind to a cleft on the GABA A receptor surface at the interface between the alpha and gamma subunits. Zopiclone does not

show subtype selectivity either but does exhibit a unique thermodynamic interaction with the benzodiazepine receptor, (this may translate into less receptor adaptation on chronic dosing, and so less tolerance and withdrawal than the benzodiazepines). Zaleplon, and zolpidem bind specifically to the alpha one sub unit at the rim of the cleft and therefore interact with amino acids in different domains to the benzodiazepines. The most prevalent GABA receptors in the brain are composed of alpha 1, beta 2, and gamma 2, subunits which are encoded by the same cluster of genes on chromosome 5. This receptor combination corresponds to over 50% of all GABA receptors in the brain and they are located mainly in the cerebral cortex.



Other substances bind to sites on the receptor

Figure 1.21: Demonstration of binding sites on the GABA A receptor

The roles of select GABA A receptor subunits (Table 1.11) in the different effects of benzodiazepines has been studied and is forming the basis of research to develop specific drugs to target these receptors for other functions rather than just sleep promotion e.g. alpha three subunit selective agonists as nonsedating anxiolytics and alpha 5 subunit inverse agonists as memory enhancers.[58] Interestingly, gaboxadol (see section 1.5) is an extrasynaptic GABA A selective agonist that targets benzodiazepine-insensitive alpha four beta three gamma receptors.

Effects of benzodiazepines	α1	α2	α3	α5	γ2	β2	β3	δ
Sedation	+	-	-	-		+		
Anxiolysis	-	+	-/+	-				
Amnesia	+							
Myorelaxation	-		+					
Motor Impairment	-	-	-					
Anticonvulsant	+	-	-	-				
Ethanol	-		+					
Effects of Anaesthetics	+					+	+	+
Anxiety					+			
Learning/Memory				+				+

Table 1.11: The roles of select GABA A receptor subunits

A molecular mechanism for hypnotic dependence, (withdrawal symptoms, rebound insomnia, anxiety and tolerance to the sedative effects) may be that there is a change in the sensitivity of the GABA receptor so that its "null efficacy" point drifts in the inverse agonist direction.[59] This may occur by down-regulation of transcription of the normally prevalent alpha-one beta-two gamma-two subunits and the reciprocal up-regulation of the expression of rarer subunits. Chronic treatment with hypnotic drugs that have less dependence potential e.g. zopiclone, zolpidem, and zaleplon appear to produce the more limited changes in GABA A receptor subunit expression.

Hypnotic efficacy

Two meta analyses confirm the short term (2-4 week) efficacy of GABA modulating pharmacotherapy in insomnia, particularly on total sleep time.[60 61] The Z drugs, zopiclone and zolpidem, have short term efficacy similar to benzodiazepine hypnotics.[62] Although zaleplon reduces sleep onset latency compared to placebo it does not seem to consistently improve the quality or duration of sleep or reduce nocturnal awakenings.[63]

Problems with the use of benzodiazepine and Z drugs

Adverse events that are reported are:

Tolerance and withdrawal (rebound insomnia)

Over sedation "hangover" effects (the following day)

Cognitive impairment

Dependence and Misuse

Tolerance and withdrawal (rebound insomnia)

Addiction is a behavioural pattern of drug abuse characterized by overwhelming involvement with the use of the drug (compulsive use), the securing of its supply, (drug seeking behaviour), and a high tendency to relapse after discontinuation. Dependence is the physiological state of neuro-adaptation produced by repeated administration of a drug necessitating continued administration to prevent the appearance of a withdrawal syndrome. When a drug causes dependence, tolerance, withdrawal and rebound can occur. Tolerance has developed when after repeated administration a given dose of a drug produces a decreased effect. Withdrawal is the term for the adverse psychological and physiological reactions to abrupt stopping of a dependence-producing drug. It is important to distinguish withdrawal from rebound. Rebound occurs when dependence occurs in patients who have taken a drug for a medically sanctioned use, the drug is suddenly stopped and their symptoms come back in an exaggerated fashion. Withdrawal, on the other hand, is what happens in those who abuse a drug and then that drug is suddenly stopped i.e. they develop withdrawal symptoms often craving dysphoria and signs of sympathetic nervous symptom activity.

Tolerance to the hypnotic effects of benzodiazepines can develop after a few weeks of use. [64] There is however evidence that this only occurs in about a 30%-45% of users. [63]

Rebound insomnia, which is more likely to happen with the shorter acting drugs at higher doses, may occur after abrupt stopping of benzodiazepine hypnotics. It

is mainly for this reason that efforts to cut down or stop can be unsuccessful. Other withdrawal effects that may occur are anxiety, perceptual distortions, hallucinations, depression and uncommonly seizures and delirium. The slow decline of blood levels with the longer acting agents means that in effect they are self tapering. Rebound insomnia can be avoided as far as possible by tapering the dose of short acting agents before stopping them.

With respect to the Z drugs, tolerance and rebound insomnia are claimed to be less common than with benzodiazepines based on the fact that zolpidem and zaleplon are more specific at the GABA receptor binding site and therefore should minimise any non-hypnotic effect, (please see later). However product characteristics of all three Z drugs warn that tolerance can occur after repeated use for a few weeks and none of the drugs are licensed for more than four weeks with zaleplon being licensed for two weeks.[65]

Over sedation

Longer acting benzodiazepine hypnotics with half-lives of over 24 hours can accumulate in the circulation when the medication is taken nightly. Residual dose related hangover effects may then occur which include daytime sleepiness, performance decrements, accidents in the home, work or while driving and contribute to falls in the elderly due to ataxia, motor incoordination and mental confusion. [66] The problems are best minimised by use of a drug with a short duration of action, given only intermittently in the lowest effective dose. [67] Elderly people are especially vulnerable to over-sedation because they eliminate the drugs more slowly, are more susceptible to CNS depression and are more

likely to be on potentially interacting drugs. [66] Half the recommended dose should be given if possible.

Zolpiclone and Zolpidem have shown residual daytime effects especially at higher doses[66] (Table 1.9). Zaleplon appears to have no detectable effects at the usual dose of 10mg on psychomotor performance or driving when taken late in the night up to 2 hours before scheduled waking time, but a four hour gap is still advised before undertaking activities requiring psychomotor coordination.

Cognitive function

Global amnesia can occur but more often episodic memory is affected. There is probably a risk of treatment related impairment of memory with both the benzodiazepines and the Z drugs.

All patients and especially those who drive or operate machinery must be warned about the risks of hangover effects if prescribed any hypnotic drugs. All hypnotics can depress respiration so should be avoided in patients with respiratory failure and obstructive sleep apnoea. All have additive effects with alcohol and other CNS depressants.

Dependence and Misuse

It is unusual to meet patients who have been medically prescribed benzodiazepines displaying drug seeking addictive behaviour but there is more evidence that benzodiazepines and the Z drugs are misused by people with alcohol dependence and polysubstance abuse. [63] Also very high doses of temazepam are sometimes swallowed, snorted or injected as euphoriants.[68]

Zolpidem has been reported to be misused as a stimulant and anxiolytic in patients without drug and alcohol problems.[69] There are no actual studies comparing the comparative risks of dependence of benzodiazepines and Z drugs.

Other drugs

Table 1.12 shows other drugs apart from antidepressants, Z drugs or benzodiazepines that have been used in the treatment of acute and/or chronic insomnia.

There is a definite need for care in prescribing hypnotic drugs, both the benzodiazepines and the Z drugs for short- term insomnia. They should be avoided in people with a history of substance abuse and then prescribed within their product characteristics. However, the recent NICE guidelines comparing the use of the Z drugs and benzodiazepines in the short term management of insomnia have been criticised because the committee has principally looked at clinical sleep parameter outcomes for insomnia and not considered the improved side effect profile of the Z drugs compared to benzodiazepines.[70]

Drug	Efficacy	Side Effects
Antihistamines including Nytol antihistamine	Sedation at first, tolerance develops quickly	Daytime sedation
Antipsychotics e.g. chlorpromazine olanzapine	Sedation can be marked Olanzapine increases SWS	Parkinsonian and anticholinergic side effects Daytime sedation Weight gain with olanzapine
Antiepileptic drugs e.g. phenobarbitone	Marked sedation	Dangerous in overdose
Chloral Hydrate	Doubtful efficacy	Tolerance and Dependence can develop
Melatonin	Lack of evidence for efficacy in insomnia	Dosage and long term side effects unknown
Herbals e.g. valerian, lavender, camomile, St John's Wort	Possible evidence for Valerian in one trial St John's Wort is an antidepressant	Interactions with other medication
Alcohol	A small amount of alcohol will help initiate sleep 'night cap'	Large amounts cause arousals due to withdrawal during the night

Table 1.12: The efficacy and side-effect profiles of other drugs used in treatment of insomnia.

The benzodiazepines they considered as short acting in the NICE guidelines all had half-lives of 6-17 hours (temazepam-lorazepam). If a drug is used with a half-life of over 4 hours it is much more likely to still be active in the brain in the morning to cause the over sedation described above e.g. affecting driving to work, hip fractures in the elderly. Indeed, Verster (2004)[71] has compared road driving effects of benzodiazepines compared to the Z drugs and found greater sedation when driving early the next morning with benzodiazepines and zopiclone but no effects at all with zolpidem and zaleplon. This would be expected as benzodiazepines also remain much longer in the brain the next day as calculated by receptor occupation.[72]

There is also now emerging evidence that there is less abuse of Z drugs than benzodiazepine hypnotics.[68] The socioeconomic cost of insomnia may be less

with Z drugs compared to benzodiazepines due to their more rapid excretion and therefore less risk of accidents the following day.[73] Also there may be a more "physiological" effect on sleep architecture in that the 'Z" drugs alter sleep architecture less than the benzodiazepines, and this may account for the fact they are easier to withdraw from with less tolerance and rebound.

Medication has a place in the management of patients with chronic insomnia, although it should preferably be used on an intermittent basis to relieve insomnia when it is at its worst, due to the potential problems with hypnotics as outlined above. However, the psychological and behavioural treatment of insomnia has become important particularly for people with chronic insomnia.

1.13 Psychological/behavioural management of insomnia

There is only limited information concerning primary insomnia's underlying pathophysiology and heritability. Deficiencies in endogenous melatonin or benzodiazepine receptors and hyperactivity of corticotrophin releasing factor neurons have been cited as potentially important to the aetiology of primary insomnia[74] and a familial propensity towards its development suggesting genetic or hereditary factors may play a part. There is however general agreement that primary insomnia is perpetuated by the interplay of cognitive and behavioural mechanisms.

Due to the potential problems with long term use of benzodiazepines and the Z drugs there has been much renewed interest in the psychological treatment of insomnia.

To introduce this field, consideration of the factors that may play a part in the development and maintenance of insomnia from a psychological basis particularly concentrating on cognitions related to insomnia are useful to consider:

1.Faulty Conditioning

Is insomnia the product of maladaptive sleep habits? Difficulty falling asleep may result from failure to establish discriminative stimuli for sleep or the presence of stimuli incompatible for sleep. These "letting down to sleep instructions"[75] are known as stimulus control therapy (SCT) , (see appendix for a copy). Stimulus control may also reduce sleep anticipatory anxiety as well as improving sleep.

2. Poor Chronobiological training

In primary insomnia it has been suggested that there may be an element of chronobiological dysfunction. For example some insomniacs go to bed early and spend excess time in bed either habitually as often in the case of older adults as a response to having slept poorly the previous night. This contributes to poor sleep efficiency. Also napping contributes to reduced nighttime sleep drive in adults. Stimulus control instructions contain elements of temporal adjustment, and may contain zeitgebers for healthy sleep. Sleep restriction therapy (SRT) is another technique that may act as a circadian harmonic and a reinforcer of homeostatic drive[76]. Stimulus control and sleep restriction

therefore overlap and the term "sleep scheduling" is sometimes used for the combination.

3. Physiological hyperarousal

There is limited evidence that some insomniacs have heightened autonomic arousal, and muscle tension. However insomniacs may display measurable neurobiological differences from normal sleepers. Differences in oxygen consumption in people with insomnia compared to controls have been found[77] and this increased metabolic rate could be viewed as a 'higher arousal set point."

Relaxation techniques and biofeedback (a visual or auditory feedback) can be provided to the patient to control pre-determined physiological parameters e.g. frontalis EMG, and can be used to decrease arousal in insomniacs. There seem to be similar treatment effects on SOL with both methods but relaxation is quicker to teach to a patient and also more applicable in a group situation.

4. Cognitive hyperarousal

The consideration of a broad range of cognitive processes is important for a full understanding of insomnia. In the 1960's and 1970s the role of "attribution" "expectation" and "perception" were emphasised. In the 1980's the emphasis was on the role of 'unwanted intrusive thoughts" and in the 1990's unhelpful beliefs about sleep were considered in more detail. The latest lines of research have begun to investigate the neural basis of cognitive arousal; the role of attentional processing in insomnia and the role of perception is being revisited.[78]

(a) Thought content and form of thought

The actual thought content of the intrusive and worrying thoughts of people with insomnia has been analysed in a few studies.

Espie (1989) used an extended version of the 'Sleep Disturbance Questionnaire" (SDQ),[79] and reported six factors, mental activity and rehearsal, thoughts about sleep, family and long term concerns, positive plans and concerns, somatic preoccupations, work and recent concerns. Harvey (2000) reported that pre-sleep cognitive activity or "pre-sleep worry " of people with insomnia could be distinguished from normal sleepers by being more focused upon worry about not getting to sleep, general worries, solving problems, the time and noises in the house, and getting less focused upon nothing in particular.[80]Wicklow and Espie (2000) obtained voice activated audiotape recordings of pre-sleep spontaneous thoughts and sleep actigraphic data from twenty poor sleepers over 3 consecutive nights[81]. There was a positive correlation between pre-sleep cognitive activity and SOL measured by actigraphy. Content analysis yielded 8 categories of pre-sleep intrusion which were divided into one of 3 factors: active problem solving e.g. rehearsing/planning events, present state monitoring e.g. thinking about sleeping /not sleeping, and environmental reactivity e.g. attending to external noises. Thinking about sleep and the anticipated consequences of poor sleep were the strongest predictors of SOL.

In the last few years the "form of thought" has been emphasised, that is rumination, worry and intrusion are distinguishable entities. "Intrusive thoughts" are spontaneous, unwanted, unbidden, uncontrollable and discrete thoughts, images or urges. While some intrusions are easily dismissed under

certain circumstances they will trigger worry and rumination "Worry" is a chain of thoughts and images, negatively affect-laden and relatively uncontrollable. Worry is more likely to occur as verbal thought, as opposed to images. Verbal thought has also been shown to be more likely to be involved in the maintenance of worry as opposed to thinking in images [82]. "Rumination" refers to the repetitive focusing on the "causes, meanings and consequences" of one's feelings and symptoms.

(b) Racing thoughts and thought management (strategies of "thought control")

Most studies have also reported cognitive arousal or "having an overactive/racing mind," as the consistent complaint of people with insomnia. Results from administering the Sleep Disturbance Questionnaire (SDQ) involves rating twelve statements for the extent they are relevant to their typical sleep pattern.[79] The thoughts most endorsed by people with insomnia were intrusive thoughts such as "My mind keeps turning over" and "I am unable to empty my mind". Ree and Harvey (2005) have examined the management of these thoughts with "thought control strategies" that categorise how the thoughts are controlled by people with insomnia, and then compared how good sleepers and people with insomnia deal with them.[83] They have developed the "Thought control questionnaire insomnia- revised (TCQI-R)" which measures these six factors of thought control:

1. Aggressive suppression, (I get angry at myself for having the thought,)
2. Cognitive distraction, (I think pleasant thoughts instead)

3. Reappraisal, (I try a different way of thinking about it)

4. Social avoidance, (I keep the thought to myself)

5. Behavioural distraction, (I keep myself busy)

6. Worry, (I dwell on other worries)

With the exception of cognitive distraction, individuals with insomnia, relative to good sleepers, more frequently used every thought control strategy. The strategies of aggressive suppression and worry, in particular, appear to be unhelpful, with the use of these strategies predicting sleep impairment, anxiety and depression. The use of cognitive distraction appeared to be helpful, with the use of this strategy predicting better sleep quality. Harvey (2003a)[84] also showed catastrophic worry was common in primary insomnia and that compared to a control group led to increased negative affect and perception of threat.

Imagery training (visualization technique to focus on some pleasant or neutral images) seeks to reduce cognitive arousal rather than somatic arousal. Harvey (2003b)[85] have demonstrated thought management via distraction with imagery versus general distraction facilitates sleep onset and reduces the discomfort associated with intrusive and worrisome thought.

Paradoxical Intention

This model of insomnia proposes that anxiety responses may be conditioned not only to external, situational cues but also to an individual's behaviour. In paradoxical treatment attempts to fall asleep are replaced by the intention of

remaining passively awake or by giving up any direct effort to fall asleep. Paradoxical intention has demonstrated efficacy in controlled trials.[86] However, Wegner (1994) has suggested a self -loading system that under certain conditions the thwarted attempt to control a particular mental state can yield the opposite of what is desired.[87] This he called "Ironic processes of mental control". More recently, Harvey (2003b) has explored the effects of suppressing pre-sleep cognitive activity i.e. thought suppression on sleep-onset latency.[85] A cohort of people with insomnia and good sleepers were allocated to either a suppression condition (suppress the thought most likely to dominate your thinking as you get into bed,) and a non suppression condition (think about anything as you get into bed, including the thought you would most likely think about before you go to sleep.) Suppression participants reported longer sleep latencies and poorer sleep quality regardless of whether they had insomnia or not. Harvey concluded that thought suppression appeared to have the opposite effect, in that it prevented sleep-onset, in a manner consistent with Wegner's theory of ironic mental control.

However when the relationship between pre-sleep cognitive activity and sleep onset latency is measured subjectively and objectively they do not always correlate.

There is a possibility therefore that pre sleep cognitive arousal is integral to sleeplessness, or that the nature of the intrusive cognitions (see later) is the critical factor.

Dysfunctional thinking

Charles Morin in the 1990's, made a major contribution to the field of insomnia research. He showed that older adults with insomnia held more unhelpful thoughts about sleep than good sleepers, were less realistic about how much sleep they required and had more negative thoughts than good sleepers at bedtime[88]. He argues that beliefs and attitudes play a critical role in insomnia. The development of cognitive therapy within multicomponent CBT for insomnia to tackle these beliefs stems from this research, and the development of a 30 item questionnaire to identify irrational affect-laden thoughts that intrude prior to sleep-onset, the Dysfunctional Beliefs and Attitudes about sleep scale (DBAS).[88]

Meta Cognition

Meta Cognition has only just being explored in insomnia. Meta-cognition refers to the thoughts and beliefs that people hold about thoughts, or the processes that are involved in keeping track of or appraising and controlling thought. Pathological worry may be maintained because the individual believes the worry may lead to positive consequences. The individual thinks that worrying in bed "helps sort out things in my mind."[89]

Attentional processing or "Sleep related threat" / Sleep Effort

"Attentional processing" research has found that the tendency to attend selectively to internal and external sleep related threats is higher in patients with insomnia than good sleepers.[90] For example, when patients with insomnia wake

up they monitor their body sensations for signs of fatigue (internal sleep related threat), and the clock to calculate how much sleep they have obtained, (external sleep related threat).

Beginning and during the night if woken up	On waking	During the day
Body signs consistent/inconsistent to falling asleep (internal)	Body sensations for signs of poor sleep (internal)	Body sensations for signs of fatigue (internal)
Environmental signs of not falling asleep (external)	The clock to see how much sleep was obtained (external)	Mood for indications of tiredness/not coping (internal)
The clock (external)		Performance for indications that attention, memory and concentration are failing (internal or external)
Needing to pass urine (internal)		

Table 1.13: Sleep related threats (internal and external)

A questionnaire has been developed to assess sleep related threat, 'The sleep associated monitoring inventory' (SAMI).[91] Tang (2007)[92] has investigated the sleep threat of "clock monitoring" further and found the monitoring of the clock by people with insomnia and good sleepers triggered pre-sleep worry but in both groups. They suggest that clock monitoring can fuel pre-sleep worry and also

exacerbate sleep misperception in people with insomnia. For examples of sleep related threat please see Table 1.13.

Perception

Distorted perception of sleep is one of the key cognitive processes in pertaining to insomnia. It was noticed and first researched in the 1970's that good sleepers underestimate wake time and overestimate total sleep time,[78] but it has also been shown that cognitive arousal and physiological arousal in healthy subjects can contribute to sleep misperception.[93]

People with insomnia tend to overestimate how long it takes them to go to sleep and underestimate how much sleep they get in total. This is called "sleep misperception" (SMP) or "subjective insomnia." Mercer 2002, measured sleep wake perception with forced waking of good sleepers and people with insomnia. They demonstrated that when people with insomnia are woken they are much more likely than good sleepers to report having already being awake.[94] This effect occurs in awakenings from REM sleep and particularly stage 2 sleep. The PSG measures of these findings correlated significantly with subjective sleep diary defined wakefulness therefore suggesting an additional mechanism underlying SMP that may involve a tendency towards interpreting sleep as wakefulness. There is evidence that monitoring for "sleep related threat" see above, cognitive arousal (e.g. worry,) and physiological arousal all fuel the distorted perception of sleep in insomnia.[90 93]

There is also evidence that SMP is not just the result of a general deficit in time estimation. Tang and Harvey (2005)[95] showed no difference in time estimation between insomniacs and good sleepers in certain time estimation tasks both in the day and their bedroom at night. The subjective perception of sleep immediately on waking may also contribute to the maintenance of insomnia. Another recent study randomly allocated patients with primary insomnia to receive either positive or negative feedback about their sleep immediately on waking on three consecutive mornings. Negative feedback impaired daytime functioning with more negative thoughts during the day, sleepiness, "safety behaviours" during the day and monitoring for sleep related threat.[96] Examples of "Safety behaviours" are "try to stop all thinking" leading to paradoxical excessive cognitive activity, "having a night cap" leading to poorer sleep continuity, "having a quiet day" leading to boredom and more time to think about the consequences of not sleeping.

How often does sleep misperception occur? The underestimation of total sleep time and overestimation of sleep latency and number of awakenings in primary insomnia has been said to be 25-50%[97] but it also occurs to some extent in insomnia associated with depression.

Armitage (1997)[98] compared a group of healthy controls and a group of patients with major depression and their objective and subjective sleep measurements. They found SOL, and TST were well correlated in both controls and those with major depression, but number of awakenings, depth and sleep quality were not.

This was also shown in a more recent study comparing objective and subjective sleep measurements in major depression.[99]

There is debate as to whether there should be a separate diagnostic category of SMP. ISCD does classify sleep misperception as a subtype of primary insomnia but DSM1V does not. Reynolds et al (1991)[100] argue that SMP represents one extreme of a continuum and accounts for only 5% of people with primary insomnia, and that diagnosis is often only based on a single PSG recording. However, Hauri and Wisbey (1992)[101] compared subjective estimates of sleep time with objective measures derived from PSG and actigraphy within the primary insomnia subtypes, psychophysiological insomnia and sleep misperception. They found those with sleep misperception have more motor activity in bed during sleep and wakefulness than do individuals with a more obvious PSG defined form of insomnia. This may suggest conventional sleep measures may not reflect the nature of sleep disturbance afflicting the so-called subjective sleep sufferers. Bonnet (1997)[102]showed that subjects with primary insomnia and sleep state misperception (SMP) had an increased metabolic rate, (although this was less so in the SMP group,) compared to controls, again perhaps supporting evidence for a separate diagnostic group.

Perlis (2001)[103] have shown that people with insomnia exhibit more high frequency EEG at or around sleep onset relative to good sleepers, whether this is due to physiological arousal or cortical arousal is unknown. They have shown that objective and subjective insomniacs have different EEG amplitude profiles or EEG sleep pathology by EEG spectral analysis and have shown that subjective insomniacs have greater alpha, sigma, and beta amplitude i.e. high frequency EEG is correlated with the extent of sleep misperception.

1.14 Multi-component cognitive behavioural therapy for insomnia

Multi-component treatment of insomnia therefore includes some or all of the following:

Sleep hygiene

Stimulus Control Treatment

Sleep Restriction

Cognitive Therapy

Imagery

Thought Stopping

Paradoxical Intention

Relaxation

Sleep Hygiene

Sleep hygiene education targets health practices e.g. (diet, exercise, substance use) and environmental factors e.g. light, noise, temperature, and mattress that may be detrimental or beneficial to sleep.

Stimulus control techniques

Stimulus control therapy is based on the premise that insomnia is a conditioned response to temporal (bedtime) and environmental (bed/bedroom) cues that are usually associated with sleep. (See appendix 1 for more details of sleep hygiene and stimulus control techniques).

Cognitive therapy

Cognitive therapy seeks to alter faulty beliefs and attitudes about sleep. The objective of cognitive therapy is to short circuit the vicious cycle of insomnia, emotional distress, dysfunctional cognitions and further sleep disturbances. Treatment targets for cognitive therapy include unrealistic sleep expectations e.g. "I must get 8 hours of sleep every night", misconceptions about the cause of insomnia e.g. my insomnia is entirely due to a chemical imbalance, amplifications of its consequences e.g. I can accomplish nothing after a poor night's sleep and performance anxiety resulting from excessive attempts at controlling the sleep process. Cognitive therapy consists of identifying patient-specific dysfunctional sleep cognitions, challenging their validity, and replacing them with more adaptive substitutes through the use of restructuring techniques such as reattribution training, de-catastrophizing, hypothesis testing, reappraisal, and attention shifting.

Relaxation therapy

Relaxation based therapies interventions are based on the observation that insomnia patients often display high levels of arousal both physiological and cognitive. Progressive muscular relaxation (a method of tensing and relaxing different muscle groups throughout the body,) and biofeedback (a visual or auditory feedback is provided to the patient to control some pre-determined physiological parameters) seek to reduce somatic arousal e.g. muscle tension. (For further information on relaxation techniques please see appendix 1)

Imagery

Attention focusing procedures such as imagery training[104] and thought stopping are intended to lower pre-sleep cognitive arousal (e.g. intrusive thoughts, "racing mind.")

This involves focusing on a pleasant image or image of six common objects when patients cannot fall asleep. Patients can be asked to visualise the shape, colour, movement and texture of the common objects.

Thought stopping

Aims to interrupt unwanted pre sleep cognitive activity by instructing the patient to repeat sub vocally, the word "the " every 3 seconds ("articulatory suppression") or to say "stop" subvocally.[105](For further information please see appendix 1)

Paradoxical intention techniques

This method consists of persuading a patient to engage in his or her most feared behaviour i.e. staying awake. It is hoped that performance anxiety will be alleviated and sleep may come more easily. (For further examples please see appendix 1)

Sleep restriction

Sleep restriction therapy consists of curtailing the amount of time in bed to more nearly matching the subjective amount of time asleep. For example if a person reports sleeping an average of 5 hours per night out of 8 hours spent in bed the

initial prescribed sleep window from initial bedtime to final arising time would be 5 hours. Then the allowable time in bed is increased by 15-20 minutes for a given week when sleep efficiency exceeds 90%, decreased by the same amount of time when sleep efficiency is lower than 80% and kept stable when sleep efficiency is between 80-90%. Adjustments are made until optimal sleep duration is achieved. (For further details please see appendix 1)

There have been some important meta-analyses and reviews in the last 10-15 years of the non-pharmacological treatment of insomnia e.g. Morin 1994[106] & 1999[107] and Murtagh & Greenwood.[108] The American Academy of Sleep Medicine Standards of Practice Committee have also published Practice Parameters for the non-pharmacological treatment of insomnia based on the 1999 review by Morin and a further review of forty eight clinical trials regarding the efficacy of the non-pharmacological treatment of insomnia.[109]

The criteria for inclusion of a study in the 1999 review were, that the main diagnosis was insomnia, that one of the treatment conditions was non pharmacological, the dependent measures included sleep onset latency (SOL), number and/or duration of awakenings, Total Sleep Time (TST), or sleep quality, and the study design had a control/comparison condition or a clinical case series evaluating a well defined treatment modality with a minimum of 10 clinical patients. It included 48 clinical trials and the two meta-analyses by Morin and Murtagh and Greenwood (see above). One hundred studies were identified but more than half were excluded as they did not meet the inclusion criteria. The main reasons for exclusion were that treatments were entirely

pharmacological, there were less than 10 patients or the subjects were of only college students.

The main findings of Morin's review showed 70-80% of people treated with non-pharmacological interventions benefited from the treatment and that three treatments met the American Psychological Association criteria for empirically supported psychological treatments for insomnia. These were stimulus control, progressive muscular relaxation and paradoxical intention.[109] (Table 1.14)

In absolute terms, these improvements are to decrease sleep onset latency to 30 minutes (from baseline to post treatment) or below, and to increase total sleep time by 30 minutes (from baseline to post treatment). These changes were sustained for at least 6 months after treatment.

Standard: Level 1 and 11 generally accepted patient care strategy
Stimulus control
Guidelines: Level 11 and 111 moderate degree of clinical certainty
Progressive muscular relaxation
Paradoxical Intention
Biofeedback
Options: Inconclusive evidence
Sleep Restriction
Multicomponent Cognitive behavioural therapy

Table 1. 14: The ASSM recommendations for psychological treatment of insomnia treatment 1999 (levels of evidence based on Sackett[110])

Note: Sleep Hygiene, Education, Imagery Training and Cognitive therapy had insufficient evidence to be recommended as a single therapy.

In 2006 Morin et al updated their 1999 review with the results of studies from 1998-2004.[51] This review was of a further 37 studies, analysed in a separate paper, using the same inclusion criteria as the 1999 metaanalysis, i.e the main diagnosis was insomnia primary or co-morbid, at least one treatment option was psychological or behavioural, the study design was a randomised controlled trial, a non randomized group design, a clinical case series, or a single subject experimental design with more than ten subjects, and had at least one sleep parameter, as a dependent variable. There were five randomized clinical trials (grade 1 evidence) four of them using CBT, since 1998. (Table 1.15)

Treatment	Study	Findings
CBT without Relaxation Relaxation	Edinger 2001	CBT>Relaxation>Placebo
Relaxation Sleep Restriction	Lichstein 2001	Relaxation>Placebo Sleep Restriction >Placebo
CBT without Relaxation	Morin 1999	CBT> Placebo
CBT with Relaxation (Group treatment)	Espie 2001	CBT>Waiting List Control
CBT with Relaxation	Jacobs 2004	CBT> Placebo

Table 1.15: Randomised clinical trials of CBT for primary insomnia from 1998-2004 (Grade 1 evidence trials)

Findings backed up the original review with empirical evidence now supporting the use of the psychological treatments: stimulus control, progressive muscular relaxation, paradoxical intention, sleep restriction and cognitive behaviour therapy for primary insomnia.

However there was little evidence to show if other complaints of people with insomnia e.g. daytime functioning were improved with treatments, this is because this is still an under researched area. There has also been shown to be improvements in insomnia of older adults, patients with chronic pain, cancer, alcohol dependence and older adults with medical or psychiatric disease using psychological and behavioural treatments as reviewed by the meta-analyses. The efficacy of psychological and behavioural interventions for insomnia in the context of hypnotic use was also reviewed and the use of psychological and behavioural treatments to support medication withdrawal.

Other aspects of both meta-analyses for the treatment of primary insomnia reviewed were:

Single or multifaceted interventions

In most of the literature there is a clear trend to combine two or more psychological treatments when treating insomnia. The most common combination involves an educational (sleep hygiene,) behavioural, (stimulus control, sleep restriction, relaxation,) and a cognitive therapy component, and is usually referred to as Cognitive Behavioural Therapy. Some studies can be grouped into the above without relaxation and others into a group without the cognitive therapy. There has been no isolation of each single treatment within the same study to measure the efficacy of each component.

Treatment format

Since the 1999 review there have been more studies carried out in a group format. There is however only one study comparing the relative efficacy of CBT implemented in a group or in individual sessions, or through self- help written materials combined with brief telephone consultations.[111] There was no between group difference between any sleep measure. In the last few years there have been studies looking at self -help, telephone consultation and internet based treatment formats.[112 113] They have had improvements at the time of therapy but have shown falling off in improvements compared to face-face consultations. Type of therapist may also be less important as long as the therapist has undergone specific training.[114]

Treatment duration

No specific recommendations in the meta-analysis have been made but the average treatment time was 5.7 consultation visits over a mean treatment period of 6.5 weeks.

Treatment durability

A very robust finding is that treatment produced changes in sleep parameters are well maintained at short, 1-3 month follow up, intermediate, 6 month, and long term, 1 year follow up. (Most studies followed up patients 1 month after treatment.) However, follow up after a year was rare and attrition rates do increase over time.

1.15 Combination of behavioural and pharmacological therapies

It is common clinical practice to provide general sleep hygiene guidelines along with a hypnotic drug when treating insomnia.

Morin (1999)[107]states that therapeutic gains in 4-8 weeks of treatment are comparable for behavioural, pharmacologic and combined treatment.

Problems with meta-analyses in chronic insomnia are:

(i) Incompatible study designs

(ii) Different outcome measures

(iii) Inconsistent criteria for the definition of insomnia

However, Smith 2002 [115] have performed a more recent comparative meta-analysis of pharmacotherapy and behaviour therapy for short term, i.e. 2-5 weeks, therapy of persistent insomnia. They compared 21 studies for primary insomnia where the outcome measures were sleep diaries. Behavioural treatments included stimulus control or sleep restriction and pharmacological agents included benzodiazepines, zopiclone, zolpidem and zaleplon.

There were no differences in magnitude between pharmacological and behavioural treatments in the measures, number of awakenings, WASO, TST, and sleep quality, but behaviour therapy resulted in a greater reduction of SOL than pharmacotherapy. However, they concluded that overall behaviour therapy and pharmacotherapy produce similar short- term treatment outcomes in primary insomnia.

Morin's 2006[51] review looks at five recent controlled studies comparing medication versus psychological therapies for primary insomnia. (Table 1.16)

In summary the current evidence shows CBT is more effective for SOL and sleep quality while medication is more effective for TST and number of awakenings.[51] Also, recently Vallieres (2005) has carried out a small pilot study on patients with chronic insomnia to investigate how CBT and medication can be integrated to optimise treatment. Three sequences were investigated for 10 weeks. CBT and zopiclone started together with the zopiclone discontinued after 5 weeks, medication alone, with the CBT then started after 5 weeks, and

CBT alone. Results showed patients who had CBT alone at the start of the study or with medication were most improved at three month follow up.

As mentioned above the long-term follow-up (i.e. 6-24 months) of behavioural and pharmacological treatment modalities show that behavioural treatments retain their clinical benefits very well over time, whereas pharmacological treatment benefits tend to return to baseline values when the medication is discontinued. What is more uncertain is the long-term outcome of patients receiving a combined approach. Although it might be expected that a combined approach may be superior to either of its single components long-term, the evidence available indicates that patients receiving both hypnotic drugs and behaviour therapy assessed at 2 years later do not retain their clinical gains at follow up as well as those treated with behaviour therapy alone.[116] This could be a negative attributional effect. Patients treated with hypnotic drugs even when combined with a behavioural intervention may attribute sleep improvements to the drug alone and such attributions may undermine the development of appropriate coping skills or discontinuing the behaviour therapy.

Treatment	Study	Findings
CBT vs Medication (temazepam) vs Combined vs Placebo	Morin 1999	Combined and Single treatments>Placebo ? Combined better
CBT vs Medication (zolpidem) vs Combined vs Placebo	Jacobs 2004	All treatments improved TST but not difference between CBT group and combined treatment group
Medication vs relaxation, imagery training, sleep hygiene	Rosen 2000	No group difference on any outcome
Modafinil vs CBT	Perlis 2004	No improvement in sleep continuity but improved day-time alertness
Benzodiazepine vs relaxation vs stimulus control vs sleep restriction	Waters 2003	Medication>all treatments

Table 1.16: Recent controlled studies comparing medication versus psychological therapies in insomnia

1.16 Clinical significance of the treatment of insomnia

This is the difference to a patient's life that the treatment of their insomnia makes rather than statistically significant improvements in objective sleep parameters, e.g. improved daytime performance, reduction in hypnotic usage, fatigue, mood, quality of life, improved concentration and memory. Do insomnia treatments make a real difference to the patient's everyday life?

Outcome measures in insomnia can be defined according to multiple measurement systems, e.g. subjective-sleep diaries, behavioural-actigraphy, and physiological-polysomnography. Daily sleep diaries remain the most widely used measure of sleep quality. Despite significant discrepancies between the subjective and objective polysomnographic measures in patients with insomnia, diaries do reflect on the subjective complaint and perception of sleep. Neuropsychological measures have sometimes been used to measure daytime functioning such as attention and concentration, information processing speed, reaction time and motor coordination, and quality of life measures are now being looked at to evaluate more fully the "functional status" of people with insomnia (discussed more fully in chapter 4). However, the current assessment tools may not be sensitive enough to detect the often subtle changes in daytime functioning related to insomnia.

It is also important to consider that participants in Randomised Clinical Trials (RCTs) for chronic insomnia have sleep recordings in a hospital sleep laboratory, are often taken off their medication and are only looked at in a research setting. Espie (2001a)[114]has performed a randomised controlled trial of cognitive behavioural therapy for insomnia (group format) in a UK general practice setting together with a reduction in medication (see chapter 4). There has also been a similar community (but in an individual format) randomised CBT versus control trial for chronic insomnia carried out also in the context of trying to decrease long term hypnotic use in general practice (see chapter 4).[117] They have both shown improvements in SOL, WASO and TST.

Espie has proposed that any realistic alternative to hypnotics must be available to patients simply, efficiently and locally. Psychologists are often not trained or interested in sleep medicine and may not be available. They felt training health visitors in cognitive behaviour therapy (CBT) for insomnia would provide the most accessible and valid approach to managing insomnia in primary care settings and they have also looked at the improvements in a clinical significant way for insomnia sufferers (see chapter 4).

There is still however little evidence that the psychological treatments for insomnia have any significant impact on daytime performance and psychological wellbeing. This is unfortunate as it is often daytime impairments in these areas that worry patients most and prompt them to seek treatment. The development of measurement of quality of life after psychological treatment for insomnia may help assess these areas further.

The following chapter in this thesis, chapter 2, describe the sleep architecture effects of two antidepressants in patients with moderate to severe depression. The effects of antidepressants on sleep in discussed in detail in this introduction but chapter 2 describes extension of this knowledge with respect to the antidepressants nefazodone and paroxetine.

Then, in the light of the knowledge of beneficial effects of nefazodone on sleep in depressed patients, it was decided to investigate whether nefazodone would have a similar effect on the sleep of patients with chronic insomnia. This is the work described in chapter 3.

In order to then include the psychological treatment of chronic insomnia it was decided to include the data from five "CBT for insomnia" treatment groups. The patients in these groups may have had primary insomnia or secondary insomnia, often due to a depressive illness, but chapter 4 brings together the results of the addition of psychological treatment to medication for this group of patients.

Chapter 2.

A comparison of the effects on sleep in depressed patients of a serotonin antagonist/re-uptake inhibitor and a specific serotonin re-uptake inhibitor

This study is a double blind placebo controlled trial, and compares the effects of two anti-depressants, nefazodone and paroxetine, on the sleep of patients with moderate to severe depression. Nefazodone was found, compared to paroxetine, to increase sleep efficiency, total sleep time and decrease number of awakenings as measured objectively by polysomnography. These effects were evident early in treatment, by day 3.

My role in the study was to recruit patients and to check the scoring of all the PSG recordings after they had been scored by the computer (visual correction.) I also analysed the data and wrote the paper for publication.

2.1 Introduction

Disturbed sleep is one of the most frequent and distressing symptoms in moderate and severe depression. It is an advantage for the patient if sleep can be improved even before the onset of antidepressant action. The use of conventional anti-depressants can have some unwelcome side effects. Tricyclic antidepressants (TCAs) can have immediate sleep promoting effects but there are other disadvantages to their use such as danger in overdose and anti-cholinergic side effects (see chapter one). The selective serotonin re-uptake inhibitors (SSRIs) are not sleep promoting and tend to exacerbate sleep

fragmentation acutely until there is a resolution because of improvement of the depressive illness.[32]

Nefazodone, a serotonin 2 antagonist/reuptake inhibitor (SARI), antagonises the reuptake of serotonin (5-HT) and noradrenaline (NA), but it also blocks the postsynaptic 5-HT2 receptor (see chapter1). Nefazodone may be unique in that it does not appear to suppress REM sleep in either healthy controls or in depressed patients, as TCAs and SSRIs produce marked suppression of REM sleep (see chapter 1). By contrast, in two studies in normal volunteers nefazadone has caused an increase in REM sleep.[40 42] However, these results were not confirmed in two later studies also in healthy human volunteers.[38 118] In normal volunteers nefazadone may also improve sleep continuity by either decreasing awake and movement time and decreasing number of awakenings[42] and this has also been shown in an open label study of nefazodone in depressed patients.[119]

The sleep effects and antidepressant efficacy of nefazodone compared to fluoxetine, a SSRI, have been compared in a multicentre trial in 125 patients with major depression.[37] Anti-depressant efficacy was comparable for both groups. With respect to sleep parameters, patients receiving nefazodone demonstrated increased sleep efficiency, and decreased number of awakenings while patients on fluoxetine demonstrated a significant decrease in sleep efficiency and a significant increase in number of awakenings compared to baseline scores. Patients taking nefazodone demonstrated an increase in total

REM sleep time in contrast to the expected REM suppression associated with fluoxetine treatment.

This study was designed to compare the effects of nefazodone and paroxetine; another commonly used SSRI, on sleep and mood in patients with moderate to severe depression, without psychotic features. It also sought to examine the claim that nefazodone can improve sleep even before the onset of antidepressant action. It was the first drug trial comparing the effects of an SARI and SSRI to use recordings carried out at home rather than in a sleep laboratory.

2.2 Method

Patients

40 depressed patients between 18 and 65 years were recruited. There were 17 males and 23 females mean age 43. Patients were recruited from general practice, a psychiatry outpatient clinic, and regional mental health teams. They were screened with a full medical and psychiatric history, a mental state examination and a physical examination. Patients had to fulfil the diagnostic criteria for DSM IV (American Psychiatric Association 1994[45]) moderate to severe depression, and score 18 or over on a Hamilton Depression Scale[120] (HRSD). (For example of this questionnaire please see appendix 2.)

Exclusion criteria included a history of schizophrenia, mania, active suicidal ideation, alcohol misuse and illicit drug use; patients unable to maintain a consistent sleep pattern e.g. shift workers or those with a current sleep/wake disorder; pregnant or nursing females and women of child-bearing age who were not taking adequate precautions against pregnancy; patients who had

participated in a clinical trial within 30 days of the study or were involved in another current clinical study at the time of assessment. Subjects who had previously taken psychoactive medication including benzodiazepines were required to undergo a two-week (or five weeks in the case of fluoxetine) washout period before entering the trial. There were six patients that had received benzodiazepines but none in the previous year. Four patients had received fluoxetine in the previous year with one ceasing for the study.

Determination of sample size

The sample size was calculated to detect the smallest clinically relevant differences in two sleep parameters (i.e. total sleep time and number of awakenings) measured by electroencephalogram with an 80% power at the 5% significance level based on variance data from a previous sleep study conducted in our laboratory.[121] The two-sample method was applied. The estimated sample size was 18 patients in each group providing valid data for at least three sleep assessments. The target sample size was extended to 22, to allow for drop-outs.

Study Design

The study used a double - blind, randomised, parallel group, single centre design. Patients gave written informed consent and the study was approved by the local research ethics committee. The acute phase of treatment either with paroxetine or nefazodone was 8 weeks, but patients who showed improvement on the Clinical Global Impression Improvement scale[122](CGI) continued to be studied clinically but without sleep measures for a further 16 weeks. (Please see appendix for an example of a CGI).

The initial daily doses of nefazodone and paroxetine were 200mg and 20mg respectively. Patients were assessed clinically at day 3, day 10, week 3, week 4, week 6 and week 8, and medication increased according to clinical response to the antidepressant. Nefazodone treated subjects were titrated to a dose between 200-600mg a day while paroxetine treated subjects were titrated to a dose between 20-40mg a day. Subjects received 8 weeks of double-blind treatment. Equal numbers of patients were randomised to receive either nefazodone or paroxetine. Adverse events were monitored at each visit and recorded. No additional psychoactive medication was allowed during the washout and treatment phase of the study and all other non-psychological/non pharmacological medications were kept to a minimum if at all possible. Figure 2.1 shows a schematic of study design.

2.3 Measurement of sleep

Objective measurement

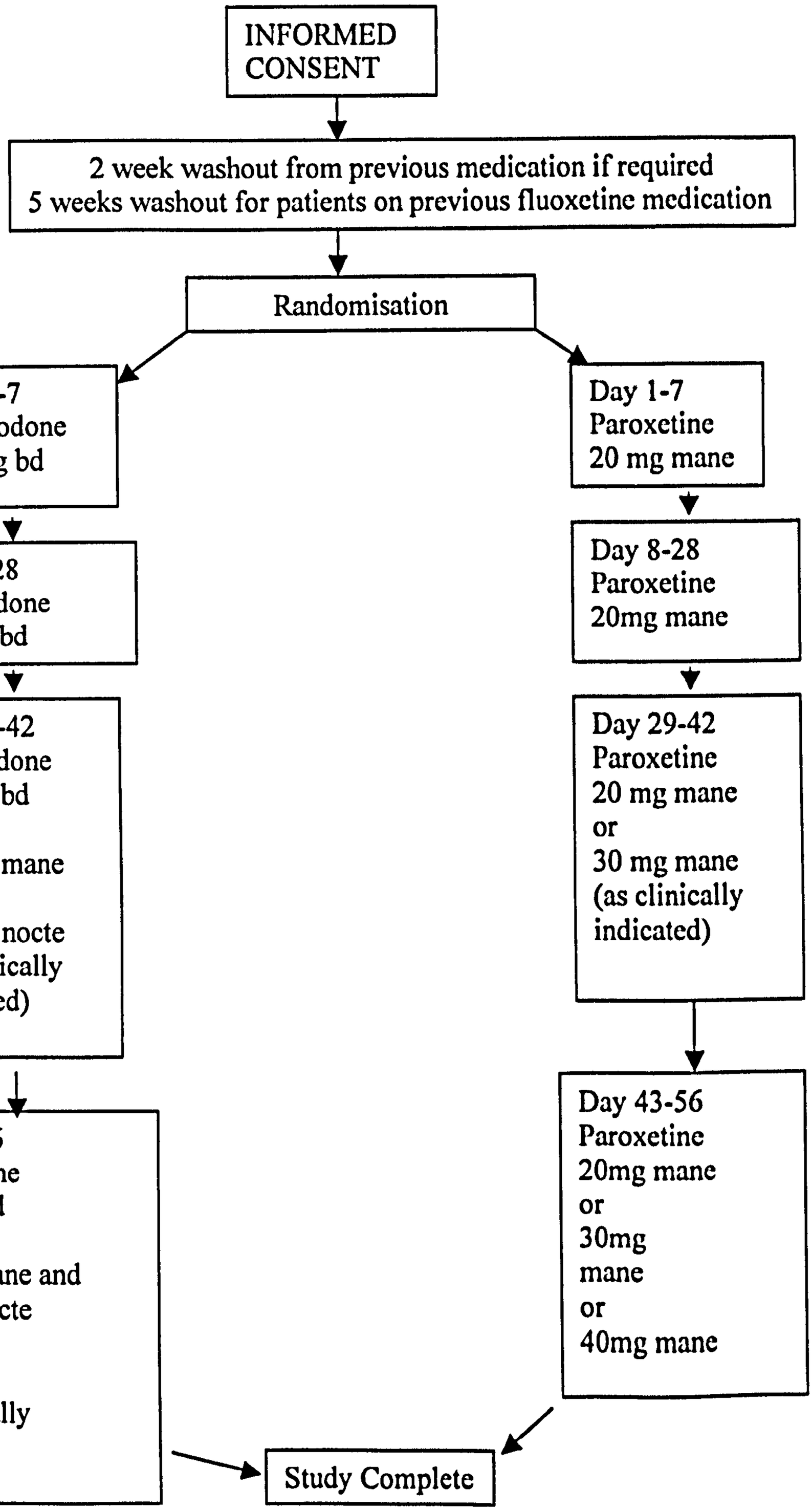
Polysomnogaphy is the gold standard method of measurement for obtaining information about timing and structure of sleep. The Rechtshaffen and Kales[5] report (see introduction) recommends minimum standards and methods of recording polysomnograms including specifications about recording equipment and electrode positions to be used. The report also recommends that assigning stages to sleep should be done using portions of recording (epochs) lasting 30 seconds each, a convenient interval when paper recordings were used and an open two pages represented 30 seconds.

Procedure for obtaining overnight recordings

Polysomnograms were recorded at home using the Medilog ambulatory system prior to treatment (baseline), night 3, night 10, and after 8 weeks of treatment. The recordings in this chapter were carried out by Dr Sue Wilson, Mrs Ann Rich and Dr Spilos Argyropoulos.

Subjects were visited in their homes during the evening and the recording equipment was attached. After the electrode impedance and the input into the recorder was checked the subjects were then left to sleep normally. The patients were asked not to bathe or shower with the equipment on but were told that otherwise they could carry on with their normal domestic routine. They were instructed to keep to their normal bedtime routine and to press the event marker on the recorder when they turned out the lights and tried to go to sleep and on waking the following morning. They were visited the next morning and the equipment was removed. On the same day the cassette from the sleep recording system was checked for the presence and quality of recording. Thereafter tapes were stored until all recordings on that subject were finished and then they were analyzed blind to both date and treatment allocation.

Figure 2.1: Schematic of study design



Sleep recordings	Baseline, night 3, night 10, week 8
Sleep questionnaires	Baseline, night 3, night 10, week 8
Sleep diaries	Baseline to day 21
Antidepressant Efficacy	Baseline, day 3, day 10, weeks 3, 4, 6 and 8

Recording equipment

The studies described in this thesis used the Medilog 9000-2 recorder, an ambulatory eight channel recorder with acquisition of the sleep recording on to an audiocassette. The recorder is small and may be worn attached to a belt while the subject is awake and moved to a position under the pillow at bedtime. The recording system allows for sensitivity of 5 μV/mm when displayed on replay with a bandwidth approximately 3dB down at 0.5 and 30Hz. A conventional 90 minute audiotape will record for 15 hours using the geared-down tape transport system, and a 120 minute tape gives 24 hours. A reliable artifact reduction system minimizes airborne and movement–related artifacts. Monitoring of incoming signals from the subject may be carried out via a socket on the recorder in order that integrity of signal may be determined before leaving the patient.

Electrodes

The International 10-20 system of electrode placement was employed.[123] The minimum requirement for sleep staging is one channel of EEG (here C4-A1). In addition EEG channel C3-O1 was used. Electroculogram (EOG) were recorded from electrodes placed above and laterally to the right eye and below and laterally to the left eye, referred to A2 as a common reference. Electromyogram (EMG) was recorded from electrodes placed on the right and left chin.

For the scalp recordings silver-silver chloride electrodes (Oxford Medical) were attached with collodion, the skin below scarified and the cup filled with electrode gel (Dracard) and then sealed over with collodion once impedance

was satisfactory. Electrodes on the face were disposable neonatal ECG electrodes (Medicotest) consisting of a small strip of chlorided silver to which electrode gel was applied, surrounded by adhesive foam and were applied to the skin with Skinpure (Nihon-Kohden) abrasive paste. Electrode impedances were measured using the Oxford Medical impedance meter and re-scarified if necessary until they were below 10 KΩ per pair.

Replaying cassettes

Cassette tapes were replayed on the Medilog 9200 replay system that displays successive 16 second sections of the recording on a computer screen. Sleep was scored at first automatically by the Medilog 9002. A sleep stage was assigned to each epoch i.e. each 30 seconds or 2 successive screens of data. Data were entered via the keyboard of a PC into a spreadsheet during replay at 20 times real time, with appropriate stops for review. A hypnogram was then constructed in the spreadsheet and the following parameters were derived from the sleep recordings:

(a) Staging time- the interval between the patient pressing the event markers (when these were omitted the sleep scorer judged these times from the EEG recording when the patient closed their eyes at night and when they opened them and started to move around the next morning).

b) Total Sleep Time, (TST) time in all stages of sleep.

c) Sleep Efficiency =%Total Sleep Time/Total Staging time.

d) Number of Awakenings were defined as those over 16 seconds in duration.

e) Sleep onset latency (S0L), the time from the patient pushing the button to start their night's sleep to the first two minutes of stage 2 sleep.

f) Duration of Stage 1, 2, 3, 4, and Rapid Eye Movement (REM) sleep (in minutes and as percentage of TST).

g) REM onset latency, the time to the first continuous 2 minutes of REM from the onset of stage 2 sleep.

h) Wakefulness after sleep onset (WASO) total time spent awake after sleep onset (in minutes).

Automatic staging with visual correction

This was carried out using the Medilog 9200 automatic staging system as above with visual correction by an experienced sleep scorer (Dr Jane Hicks).

Although the Medilog system uses the Rechstaffen and Kales criteria correction of the automatic scoring by an experienced observer is necessary because misclassification of epochs can occur.

Some of the reasons the automatic scoring system misclassifies data are enumerated below:

1) REM can be overestimated due to the fact that EMG level is averaged over the night and in a subject that wakes a lot and therefore has a high average EMG, short term drops in EMG sufficient to cause a classification into REM are frequent and thus REM is over estimated.

2) Stage I sleep is identified by the absence of alpha rhythm, high EMG, sleep spindles and delta activity, so quiet waking in a subject with little alpha rhythm

is confused with stage 1, and in a subject with poorly defined sleep spindles such as in depression, with stage 2.

3) Some movement artifacts are confused with EEG delta activity particularly teeth grinding and scratching.

It should also be emphasized that scoring according to the Rechtshsaffen and Kales criteria is difficult when examining a depressed patient's EEG. They have poorly defined sleep spindles and less obvious sleep stages. (Very recently there has been a new scoring system derived by the ASDA that may help to improve scoring criteria.)

In general, REM sleep, waking and stage 1 sleep show the least agreement with visual scoring and require the most correction. Once corrected this system produces a hypnogram and sleep statistics can be derived.

Outcome Measures:

Objective measurements

Primary objective sleep variables were:

Sleep Efficiency, Total Sleep Time and Number of Awakenings.

Secondary sleep parameters were also measured.

Subjective measurements

Subjective measures of sleep used in this study were:

1) St Mary's Hospital Sleep questionnaire (SMHSQ) evaluations [124] were made on the mornings after the baseline night recordings.
2) The SMHSQ and Leeds Sleep Evaluation Questionnaire (LSEQ) [125] were performed at days 3 and 10 and week 8 of treatment after the overnight recording.
3) The patients also kept a diary recording the quality of their sleep for the first 21 days of treatment

(Copies of these questionnaires appendix 2)

Answers to the SMHSQ were obtained on the morning after the baseline recording. Thereafter the SMHSQ and the LSEQ were performed at days 3 and 10 and week 8 of treatment. Patients kept a diary of sleep quality and number of awakenings for the first 21 days of treatment.

Subjective measures of depression, HRSD, Montgomery Asberg Depression ratings scale (MADRS),[126] and a Clinical Global Impression score (CGI)[122] were carried out at baseline, days 3,10, and weeks 3,4,6, and 8. Please see appendix 2 for copies of these questionnaires.

2.4 Statistical Analysis

Statistical Analysis of the objective sleep data was carried out using STATA version 7.0 for Windows[127]. Information on the variables was collected at baseline and at three time points after initiation of the therapy (i.e. day 3, day 10 and week 8). Descriptive statistics were derived for each of the variables. Tests for normality showed that the variables stage 1, stage 3, sleep onset latency, REM onset latency, and wakefulness after sleep onset were not normally distributed. The values for stage 1 sleep and sleep onset latency, and

wakefulness after sleep onset were normalized by logarithmic transformation, whereas it was necessary to use the square roots of the values for stage 3 sleep, REM onset latency, and wakefulness after sleep onset to produce normally distributed data. Complete data sets i.e. four sleep assessments, were available on 29 individuals and this resulted in an unbalanced design. Consequently a sequential fitting of the different sum of squares was used. Split plot analysis of variance, (split plot ANOVA) was used to investigate the effects of the two drugs on all the sleep variables. This analysis separates the variance ascribable to pre-treatment differences between the two treatment groups, due to the effect of time, due to the interaction between time and treatment and due to the effect of the treatments themselves.

Dr Spilios Argyropoulos analysed the subjective data and is a co-author on the paper which details the results of this study (see appendix).[128] As regards the subjective sleep data, descriptive statistics, comparison tests at days 3, 10 and week 8 and ANOVA were performed on the scores of LSEQ, the items 5, 6, 9-11 and 13 of SMHSQ and the sleep items of the HSRD. Values from the daily diary of sleep quality were analyzed with descriptive statistics and scrutinized for possible trends in the data. An average score for each week of the study was compared for the two groups.

Data from HRSD, MADRS and CGI severity and improvement scales were tabulated using both the observed values and with last observation carried forward (LOCF) in the whole (intent to treat; ITT) group. Number of responders (50% or more reduction on baseline HSRD) and remitters (HSRD

less than or equal to 8) were tabulated for each treatment group. Total scores for the rating scales were analyzed using ANOVA, first at baseline and on the change from baseline at the end of the specific weeks and end-point (subject's last available observation).

Adverse events were cross-tabulated by treatment, severity and clinical estimate of relation to study medication, to detect any evidence of drug-related trends or increased incidence.

2.5 Results

Forty patients (23 females, 17 males) were randomised to nefazodone (n=20) or Paroxetine (n=20). Demographic data and past psychiatric history data, including co-morbidity, are presented in Table 2.1. There were no significant differences between the groups in these variables. The number of patients that completed the study and the reasons for early discontinuation are presented in Table 2.2

Table 2.1: Baseline demographic and clinical data

Baseline Characteristic	Nefazodone (n = 20)	Paroxetine (n = 20)
Age (years) (mean, s.d.)	42.75 (11.93)	42.95 (10.12)
Median (range)	46 (18-62)	44.5 (23-59)
Male (%)	8 (40)	9 (45)
Women (%)	12 (60)	11 (55)
Past History of Depression (%)	12 (60)	11 (55)
Previous anti-depressants (%)	16 (80)	13 (65)
Number of previous episodes (mean, s.d.)	2.11 (3.75)	2 (4.01)
Age at onset of first episode (years) (mean, s.d.)	32.11 (13.09)	31.6 (12.34)
Length of previous episodes (weeks) (mean, s.d.)	23.33 (16.91)	37.33 (27.39)
Length of current episode (weeks) (mean, s.d.)	50.65 (57.80)	42.6 (45.75)
Co-morbidity (%)		
Dysthymia	4 (20)	2 (10)
Anxiety Disorders	5 (25)	2 (10)
Chronic Physical Conditions	2 (10)	5 (25)

Table 2.2: Reasons for discontinuing study

Reason for discontinuation	Nefazodone 8 week sleep study	Paroxetine 8 week sleep study
Completed study (%)	15 (75)	17 (85)
Non-completers (%)		
Adverse experience	4 (20)	1 (5)
Lost to follow-up	1 (5)	
Lack of efficacy		2 (10)
Total discontinuations	5 (25)	3 (15)

Patients excluded from the analysis were:

Patient 1 - because they only completed the baseline assessment.

Patient 12 - completed baseline and day 3 assessments, but the day 10 recording was technically unsatisfactory.

Patient 18 - because the baseline recording was technically unsatisfactory.

In addition, patient 15's day 3 recording was technically unsatisfactory but baseline, day 10 and week 8 were included. Patients 7,10,11,25 and 27 had no week 8 recording as they left the study. In the paroxetine group, 4 patients at day 3 and 1 patient at day 10 had no REM sleep at all. In these patients the REM latency was taken to be the staging time minus sleep onset latency.

The mean nefazodone dose (standard deviation) used in the study was 495mg/day (82.6) and for paroxetine it was 29.5mg/day (8.9). These doses were well within the therapeutic range advised for these drugs for the treatment of depression

Objective sleep data

Table 2.3 shows the polysomnographic data of sleep parameters: sleep initiation, length, maintenance and sleep architecture with the results of the split plot ANOVA statistical analysis.

There were significant pre-treatment differences between the two treatment groups on nearly all the sleep measures with sleep in the paroxetine group being generally worse. These pre-treatment differences occurred entirely by chance because treatment allocation was random. As described in the methods section, this baseline difference was taken into account when assessing the treatment effects by using the split-plot ANOVA.

There were significant treatment effects on total sleep time, sleep efficiency, number of awakenings, wakefulness after sleep onset, stage 1 sleep, REM latency, and REM sleep (see figures 2.2-2.8). There were non-significant drug effects on slow wave sleep (i.e. stage 3&4 sleep), stage 2 sleep and sleep onset latency.

Table 2.3: Objective (EEG) Sleep Data

Sleep Measure	Nefazodone mean (sd)				Paroxetine mean (sd)				ANOVA (Treat effect)	
	N=19	N=19	N=18	N=14	N=18	N=17	N=18	N=16	P value	F value
	baseline	Day 3	Day 10	Week 8	baseline	Day 3	Day 10	Week 8		
Sleep onset latency (mins)	31(32)	33(29)	35(46)	20(9)	33(32)	55(48)	36(25)	41(35)	ns	
%sleep efficiency	81(9)	85(10)	84(12)	84(11)	78(11)	71(13)	77(9)	78(8)	0.005	11.49
Number of awakenings	13(8)	13(6)	10(6)	14(9)	17(8)	16(9)	18(8)	24(13)	0.025 treatment 0.0097 time 0.03 time/treatment	7.51
%stage 1	10(6)	9(8)	6(4)	6(4)	10(7)	11(8)	10(6)	13(7)	0 025	6.33
%stage 2	45(10)	46(9)	46(9)	46(12)	40(13)	45(13)	45(9)	40(9)	ns	
%stage 3	7(4)	8(5)	9(6)	11(8)	7(4)	9(8)	8(5)	7(4)	ns	
%stage 4	8(6)	6(5)	6(6)	6(8)	9(10)	10(13)	9(11)	6(10)	ns	
% REM	21(6)	24(5)	26(8)	23(6)	20(7)	7(8)	12(6)	6(6)	0 01	29.4
REM latency	78(36)	59(28)	61(42)	62(34)	73(45)	278(113)	227(120)	173(52)	0 001	133 05
%Wakefulness after Sleep onset WASO	14(42)	9(41)	10(40)	14(60)	18(58)	22(54)	21(52)	16(37)	0.025	
Time in bed TIB	474(61)	482(60)	466(73)	473(65)	479(83)	472(79)	458(64)	495(56)		
Total Sleep Time TST	383(48)	409(67)	389(40)	396(53)	370(63)	334(76()	352(610	388(70)	0 05	5.05

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Figure 2.2: Total Sleep Time

Results of Split-plot ANOVA of total sleep times – Nefazodone vs Paroxetine, and graph of mean total sleep times at baseline, day 3, day 10 and week 8.

Source	Seq. SS	Df	MS	F	Prob > F
Model	171422.39	32	5356.95	1.73	0.037
Pre-treat	42830.27	1	42830.27	11.69	<0.005
Treatment	**18500.96**	**1**	**18500.96**	**5.05**	**< 0.05**
Error (1)	95249.16	26	3663.43	1.18	0.30
Time	7021.45	2	3510.72	1.13	0.33
Time*treat	7820.55	2	3910.27	1.26	0.29
Error (2)	167193.34	54	3096.17		
Total	338615.72	86	3937.39		

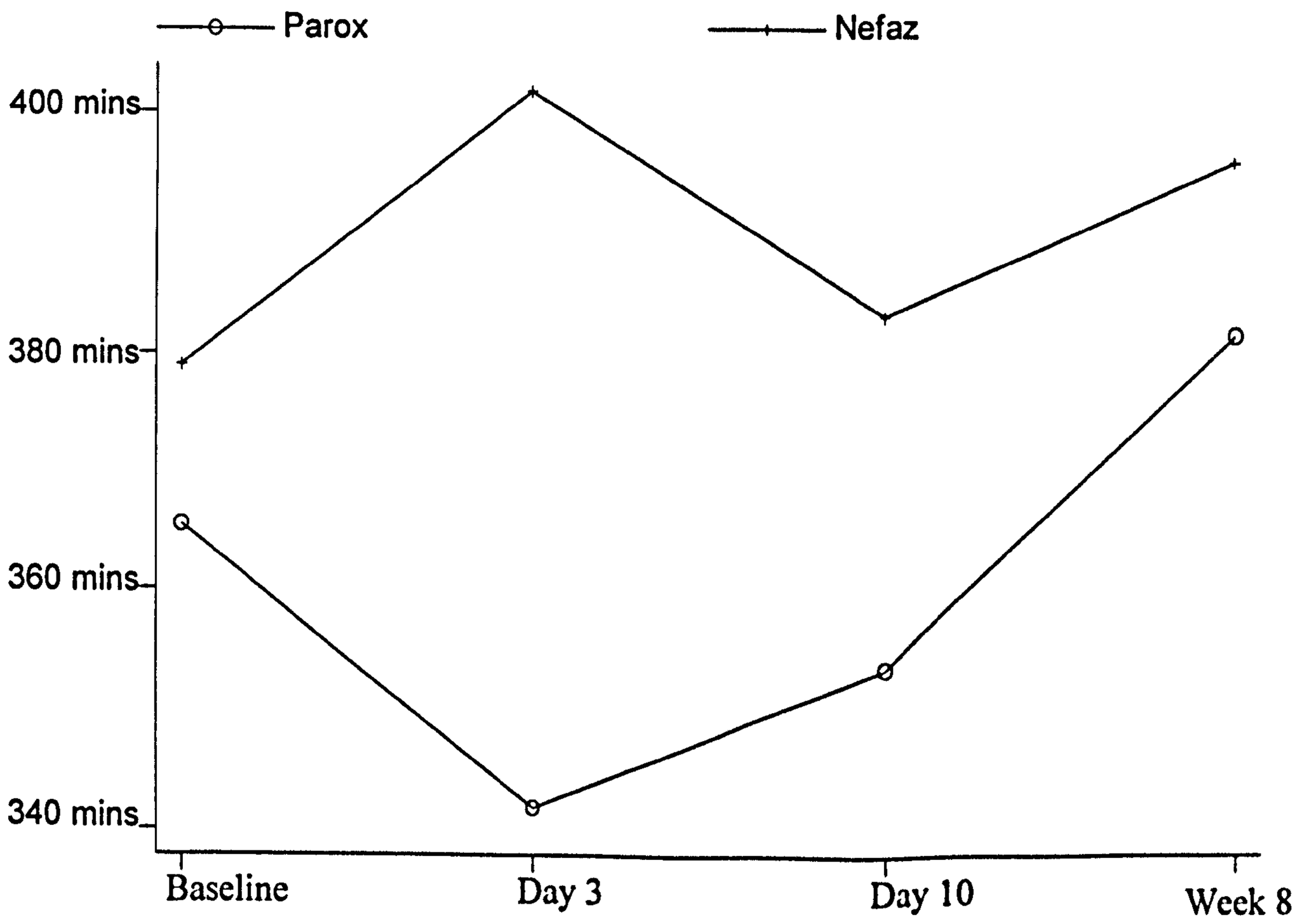


Figure 2.3: Mean sleep efficiency

Results of Split-plot ANOVA of sleep efficiency – Nefazodone vs Paroxetine, and graph of mean sleep efficiency at baseline, day 3, day 10 and week 8.

Source	Seq. SS	Df	MS	F	Prob > F
Model	6074.33	32	189.82	2.05	0.0098
Pre-treat	1184.3	1	1184.3	9.98	< 0.005
Treatment	**1362.9**	**1**	**1362.9**	**11.49**	**< 0.005**
Error (1)	3084.5	26	118.6	1.28	0.22
Time	144.89	2	72.45	0.78	0.46
Time*treat	297.79	2	148.90	1.61	0.21
Error (2)	4999.67	54	92.59		
Total	11073.99	86	128.77		

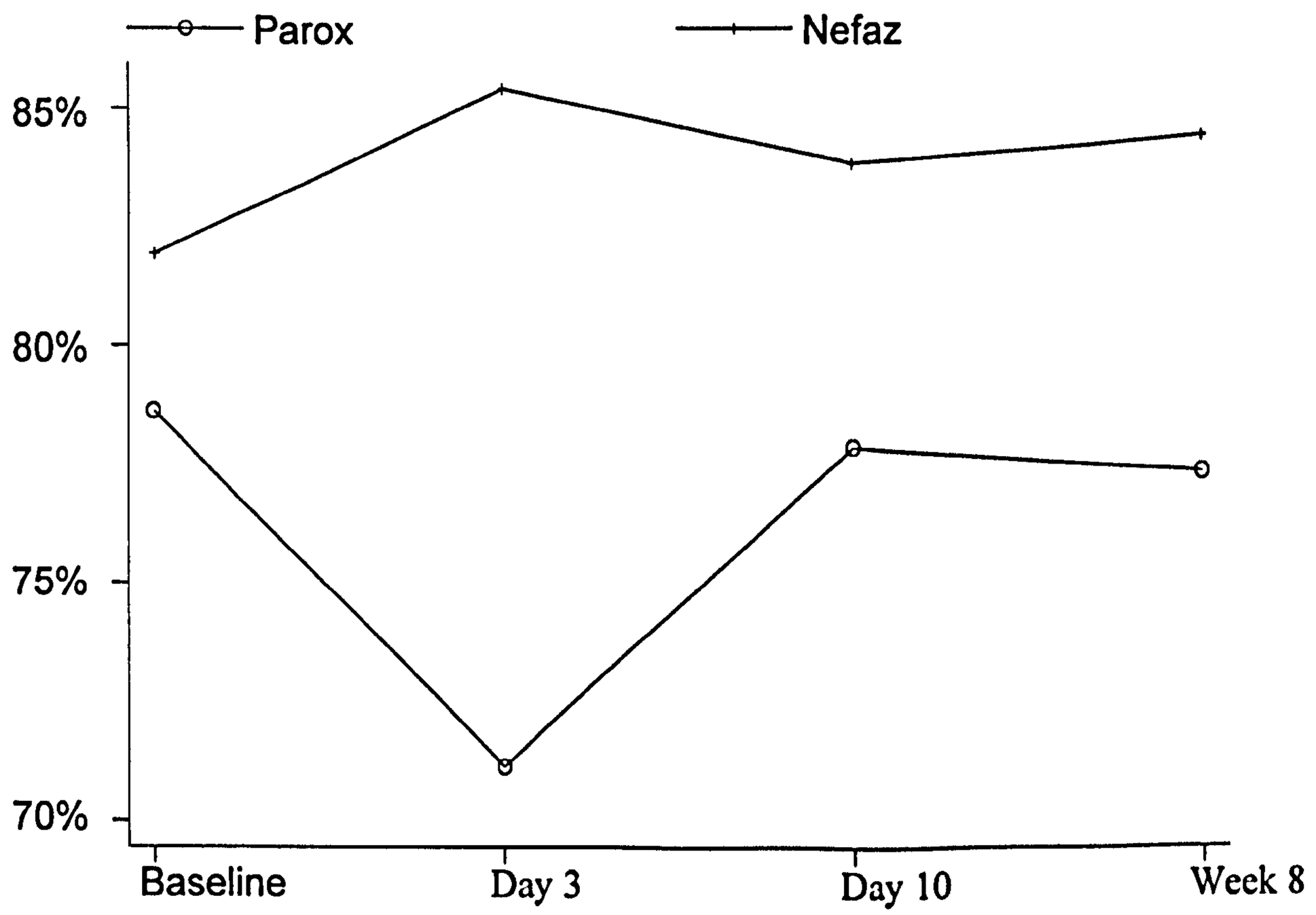


Figure 2.4: Number of Awakenings

Results of Split-plot ANOVA of number of awakenings – Nefazodone vs Paroxetine, and graph of mean number of awakenings at baseline, day 3, day 10 and week 8.

Source	Seq. SS	Df	MS	F	Prob > F
Model	5656.65	32	176.77	3.5	0.0000
Pre-treat	1593.99	1	1593.99	16.8	< 0.001
Treatment	**712.07**	**1**	**712.07**	**7.51**	**< 0.025**
Error (1)	2466.66	26	94.87	1.88	0.025
Time	510.44	2	255.22	5.06	0.0097
Time*treat	373.50	2	186.75	3.7	0.031
Error (2)	2724.07	54	50.45		
Total	8380.71	86	97.45		

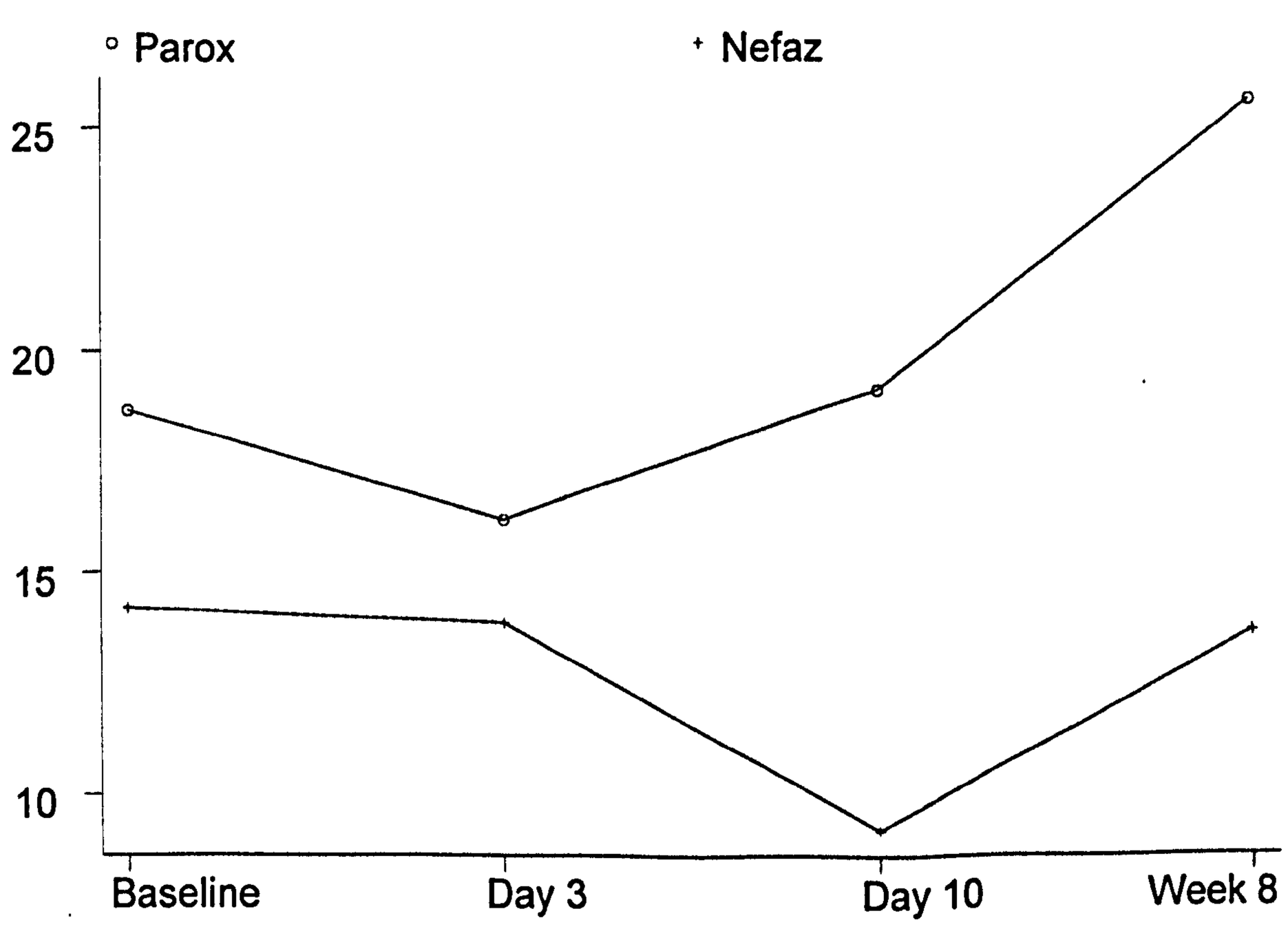


Figure 2.5: REM Onset Latency

Results of Split-plot ANOVA of REM onset latency – Nefazodone vs Paroxetine, and graph of mean REM onset latency at baseline, day 3, day 10 and week

Source	Seq. SS	Df	MS	F	Prob > F
Model	1405.05	32	43.91	4.95	0.0001
Pre-treat	15.86	1	15.86	1.89	n.s.
Treatment	**1113.69**	1	**1113.69**	**133.05**	**< 0.001**
Error (1)	217.67	26	8.37	0.94	0.55
Time	15.47	2	7.74	0.87	0.42
Time*treat	42.36	2	21.18	2.39	0.10
Error (2)	479.14	54	8.87		
Total	1884.2	86	21.91		

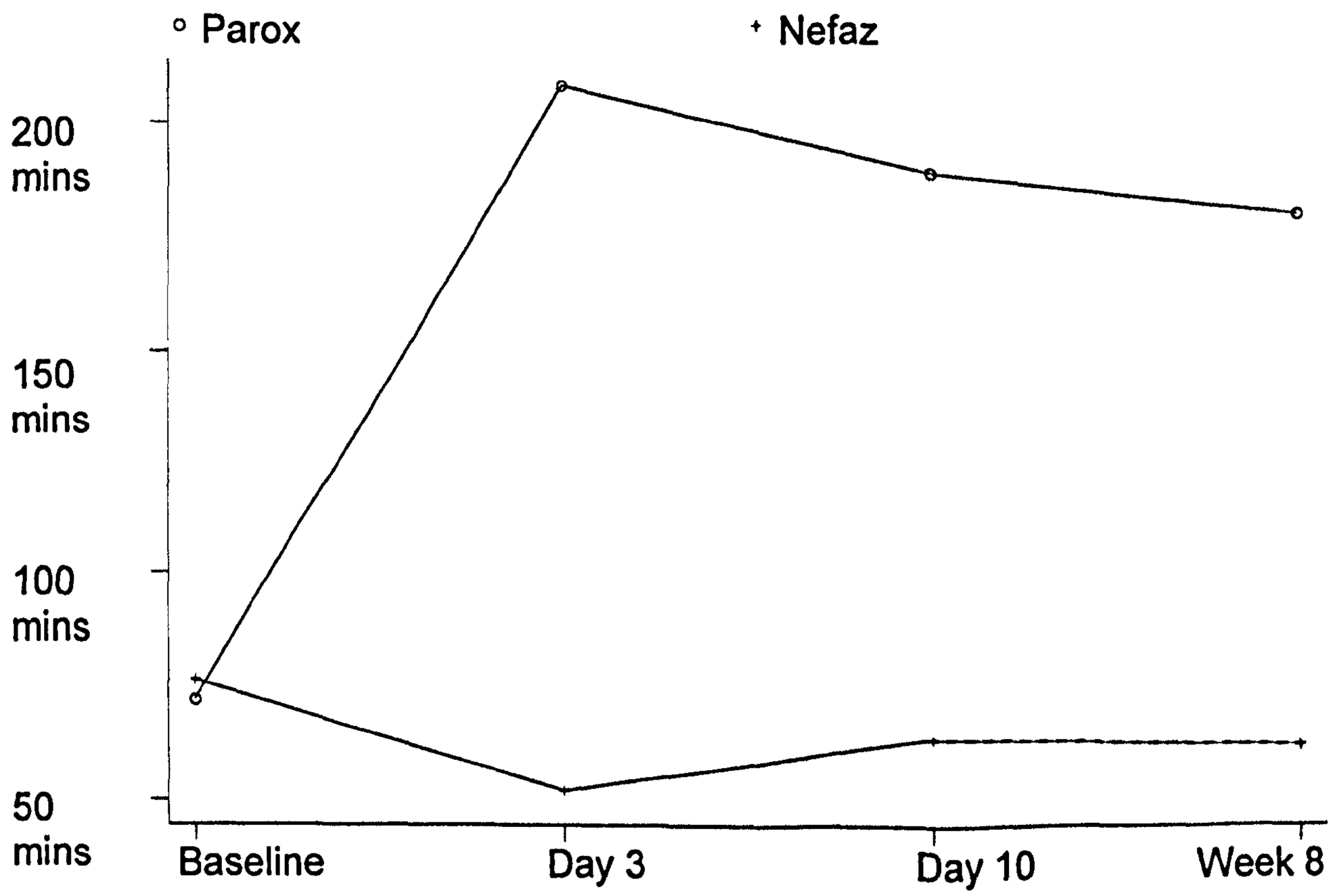


Figure 2.6: Stage I sleep

Results of Split-plot ANOVA of Stage 1 sleep – Nefazodone vs Paroxetine, and graph of mean Stage 1 sleep at baseline, day 3, day 10 and week 8.

Source	Seq. SS	Df	MS	F	Prob > F
Model	37.33	32	1.17	5.33	0.0001
Pre-treat	12.31	1	12.31	17.9	< 0.001
Treatment	**4.24**	**1**	**4.24**	**6.33**	**< 0.025**
Error (1)	17.47	26	0.67	3.07	0.0002
Time	1.16	2	0.58	2.66	0.079
Time*treat	2.14	2	1.07	4.88	0.011
Error (2)	11.81	54	0.22		
Total	49.14	86	0.57		

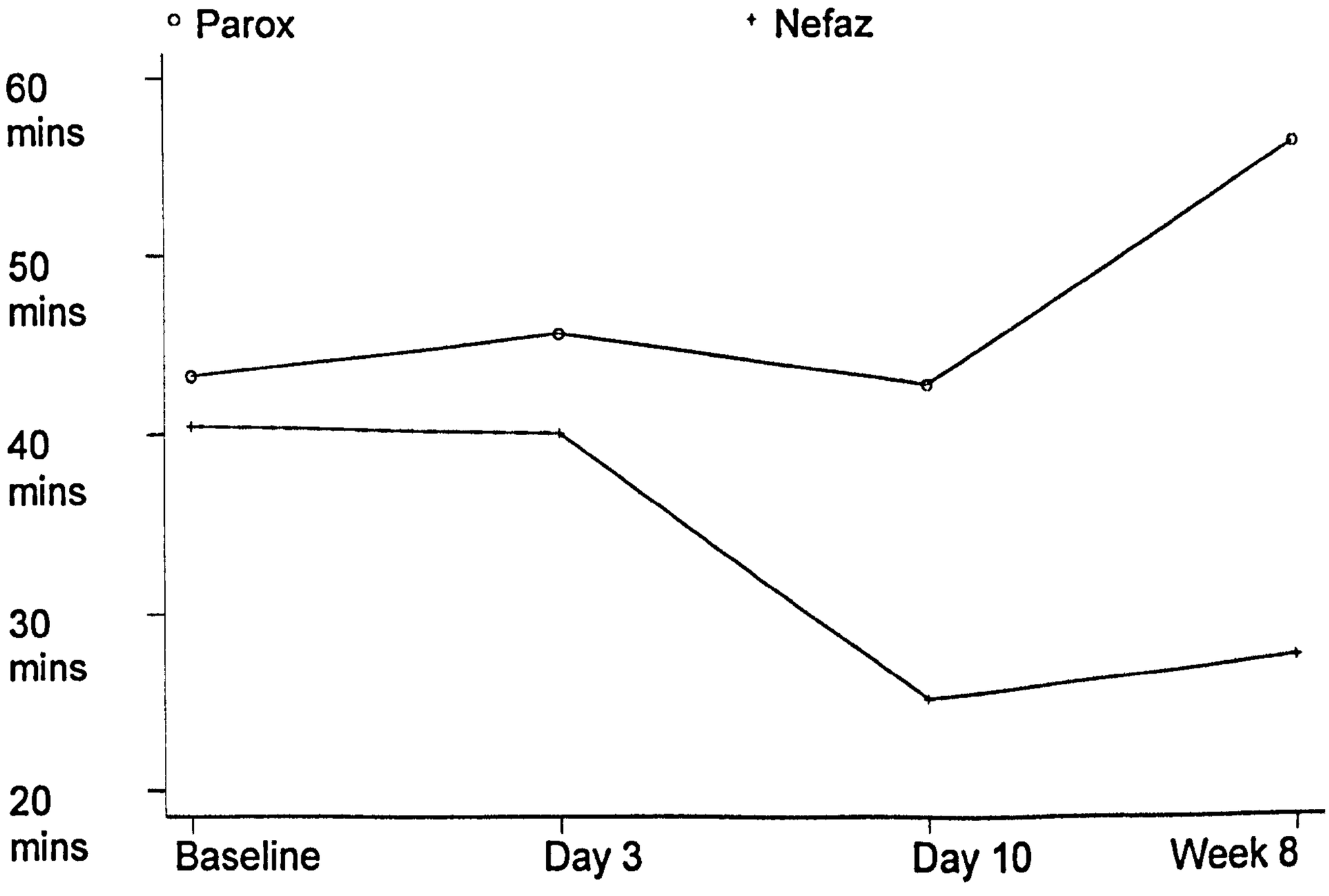


Figure 2.7: WASO

Results of Split-plot ANOVA of Wakefulness after sleep onset (WASO) – Nefazodone vs Paroxetine, and graph of mean WASO at baseline, day 3, day 10 and week 8.

Source	Seq. SS	Df	MS	F	Prob > F
Model	566.89	32	17.72	2.62	0.0009
Pre-treat	141.19	1	141.19	11.9	< 0.005
Treatment	**85.01**	**1**	**85.01**	**7.2**	**< 0.025**
Error (1)	308.36	26	11.86	1.76	0.041
Time	16.66	2	8.33	1.23	0.30
Time*treat	15.68	2	7.84	1.16	0.32
Error (2)	364.52	54	6.75		
Total	931.41	86	10.83		

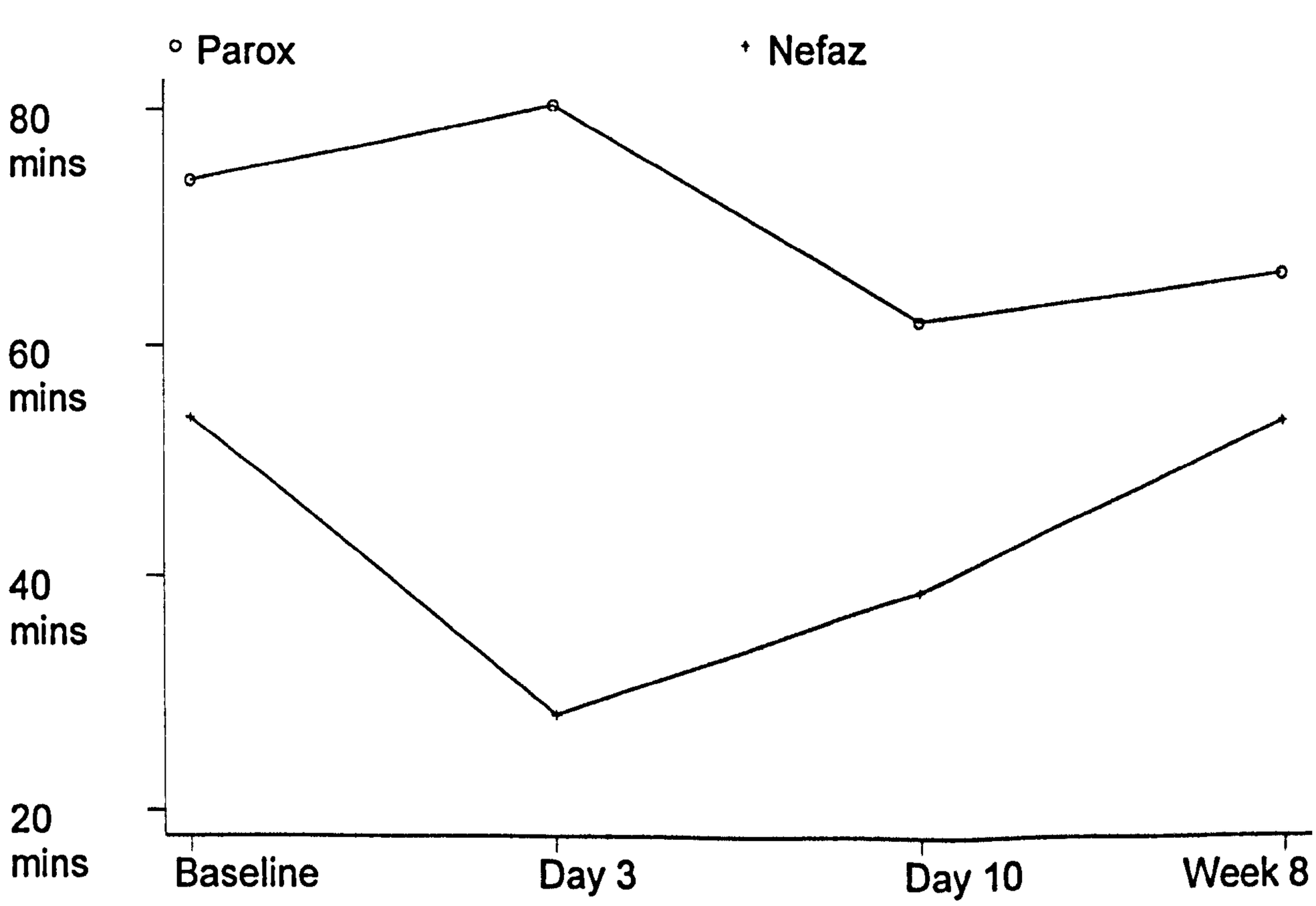
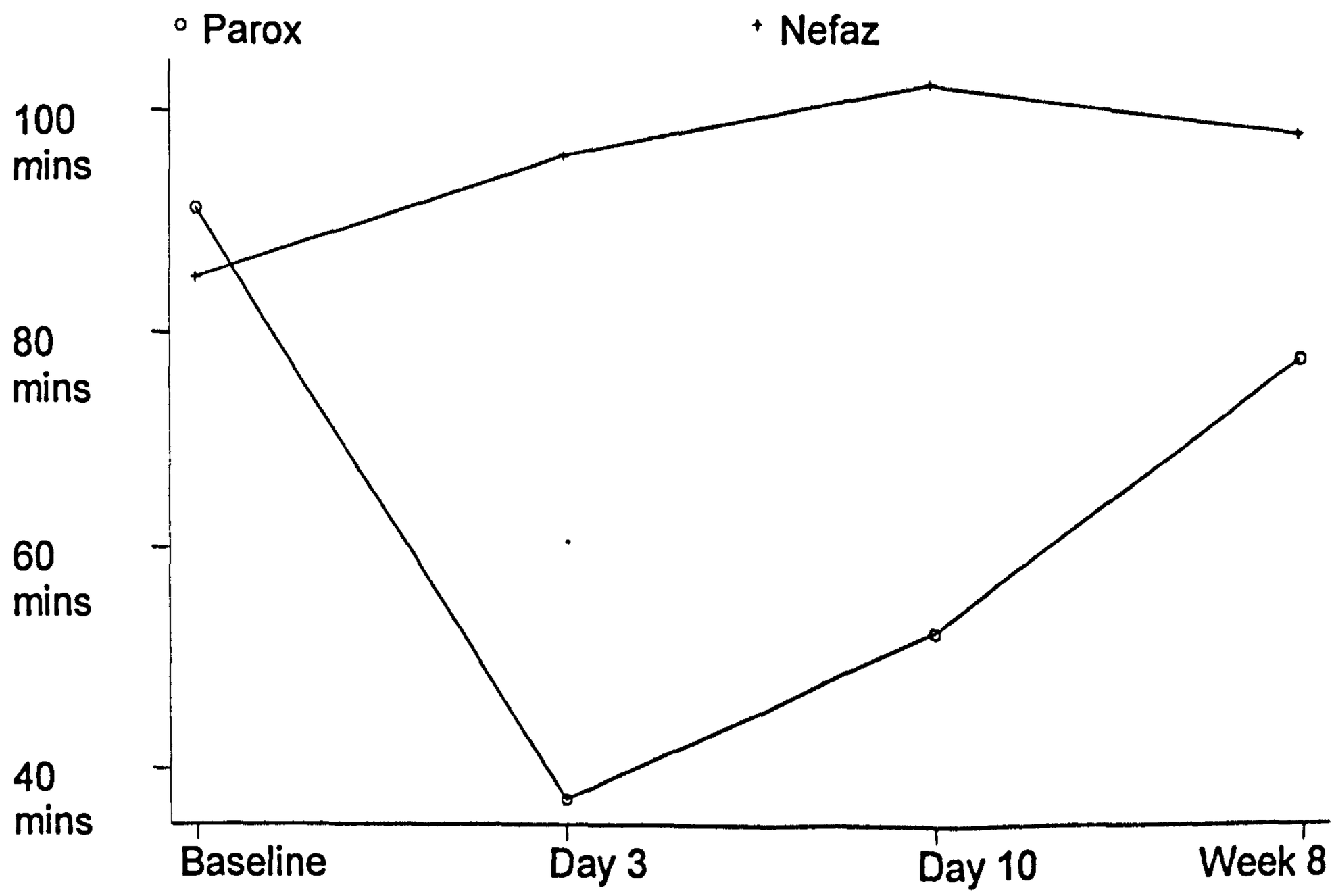


Figure 2.8: REM sleep

Results of Split-plot ANOVA of total REM sleep – Nefazodone vs Paroxetine, and graph of mean total REM sleep at baseline, day 3, day 10 and week 8.

Source	Seq. SS	Df	MS	F	Prob > F
Model	91821.75	32	2869.43	2.39	0.0023
Pre-treat	695.17	1	695.17	0.49	n.s.
Treatment	**41623.23**	**1**	**41623.23**	**29.4**	**< 0.001**
Error (1)	36878.04	26	1418.39	1.18	0.30
Time	6778.55	2	3389.28	2.82	0.068
Time*treat	5846.76	2	2923.38	2.43	0.097
Error (2)	64903.36	54	1201.91		
Total	156725.10	86	1822.38		



Figures 2.2, 2.3 and 2.7 demonstrate the significant drug effects on total sleep time, sleep efficiency, and wakefulness after sleep onset, with nefazodone improving these and paroxetine worsening them early in treatment but both drug groups returning towards baseline by 8 weeks.

Number of awakenings (Figure 2.4) and Stage 1 sleep (Figure 2.6) also showed significant treatment effects and these were more obvious at 8 weeks, with both measures being increased in the paroxetine group. Number of awakenings showed a significant time x treatment effect, with the differences between the two treatment groups increasing as time on treatment increased. There was a similar time x treatment interaction on stage 1 sleep with the paroxetine group having significantly more stage 1 sleep over time when compared to the nefazodone group.

There were highly significant treatment differences on REM sleep, with paroxetine increasing REM latency and decreasing the total amount of REM sleep throughout the 8 weeks of treatment. Figure 2.5 shows that paroxetine dramatically increased REM latency by day 3 of treatment whereas the nefazodone group showed a slight decrease in REM latency and that this difference between the two treatment groups was maintained throughout the trial period. Figure 2.8 shows that the paroxetine group had a rapid reduction in the total amount of REM sleep by Day 3 whereas the nefazodone group had a

modest increase in REM sleep. The differences in total REM sleep time between the two groups tended to decrease over the 8 weeks of the trial.

Neither slow wave sleep nor stage 2 sleep showed significant time or group differences.

Subjective sleep data

Subjective data from the SMHSQ were not distributed normally and there was a significant difference between the two treatment groups at baseline.

Changes from baseline scores were derived for all patients and these were found to be distributed normally and thereafter used in subsequent testing. A significant difference was found at night 3 for sleep quality (item 5: how well did you sleep? $t = 2.12$, d.f. = 36, $p = 0.04$) with the nefazodone group showing greater improvement from baseline. On the ANOVA there was a treatment effect for sleep quality ($p = 0.042$) and for sleep depth ($p = 0.042$) with the nefazodone group showing more improved scores on both.

There was no significant treatment effect on the variables of LSEQ. The four factors of the LSEQ are:

Factor 1: Getting to Sleep

Factor 2: Sleep Quality (a higher score shows a worse quality of sleep)

Factor 3: Morning Tiredness

Factor 4: Behaviour on Awakening (clumsiness and tiredness in the morning)

Factor 4 "Behaviour on Awakening" showed a trend for less clumsiness and tiredness in the morning with paroxetine but more with nefazodone. The differences from baseline, however, were small. The week-by-week analysis of the sleep diary averages for sleep quality (how well I slept) and continuity (how many times did you wake up?) and the HSRD sleep items were not significantly different in the two groups.

Adverse Events

There were no serious adverse events related to either of the medications. One patient on paroxetine was hospitalized for worsening of her primary diagnosis of depression and emerging suicidal ideation, following the day 3 visit. The randomization code was broken and the patient was continued on open-label paroxetine and made a good recovery. Table 2.4 shows the non-serious side-effects attributable to the medications. These were similar to those described in previous reports.

Anti-depressant efficacy

Response was defined as a 50% or greater reduction from the initial HRSD score, whereas remission was defined as a final HSRD score of 8 or less. There was no significant difference between the two medications in these variables. At week 8, 11 patients on nefazodone and 16 patients on paroxetine were responding to treatment. At the end of the 24-week study, a total of 12 in the nefazodone group and 14 in the paroxetine group had responded to treatment, while 9 patients on nefazodone and 12 patients on paroxetine were

classified as remitters. Between 8 and 24 weeks, 2 patients in the paroxetine had experienced a worsening of depressive symptoms.

There were no significant differences between the two drugs in HSRD, MADRS, CGI Severity and Improvement scales, either on observed data or on Last Observation Carried Forward (LOCF) data. Data from the MADRS questionnaire, (which has only one question about sleep,) were as follows (observed cases): nefazodone group baseline 27.5 (s.d. = 4.1), 8 weeks 13.0 (s.d. = 7.7); paroxetine group baseline 27.1 (s.d. = 3.5), 8 weeks 8.4 (s.d. = 6.2).

Table 2.4: Number of non-serious adverse events occurring in more than 5% of patients (% of patients reporting)

Type of adverse event	Nefazodone	Paroxetine
Stomach upset, nausea, vomiting, diarrhoea	13 (40)	25 (65)
Headache, migraine	15 (50)	15 (50)
Tiredness, asthenia	9 (40)	13 (55)
Drowsiness, sedation	11 (40)	5 (25)
Dry mouth	6 (25)	7 (35)
Dizziness	5 (25)	3 (15)
Flu-like symptoms	2 (10)	4 (15)
Unsteadiness, giddiness, ataxia	6 (25)	3 (15)
Sweating	0	7 (35)
Sexual dysfunction	0	5 (20)
Light-heartedness, spaced-out feeling	1 (5)	4 (20)
Rash, itching	1 (5)	4 (20)
Tremor, Shakiness	0	4 (20)
Constipation	1 (5)	3 (15)
Other (each reported in only one patient)	13	12

2.5 Discussion

Baseline sleep architecture changes in these depressed patients, compared to normal sleepers, were low TST and sleep efficiency, shortened REM latency and increased Stage 1 sleep. This was to be expected. However the two groups sleep parameters were different at baseline with patients in the paroxetine group having poorer sleep .

There were statistically significant differences between patients prescribed nefazodone and paroxetine (taking into account pre-treatment differences between the two groups). Patients taking nefazodone had increased total sleep time, increased sleep efficiency and decreased number of awakenings compared to those taking paroxetine. These findings were evident early in treatment i.e. from day 3.

Rush (1998), in a multi centred trial compared the effects of nefazodone and fluoxetine on the sleep of outpatients with major depressive disorder at 2, 4, and 8 weeks of treatment.[37] They found nefazodone and fluoxetine were equally effective in reducing depressive symptoms, but nefazodone increased sleep efficiency and reduced the number of awakenings over the 8 weeks of treatment. Fluoxetine but not nefazodone, prolonged REM latency and suppressed REM sleep. They also showed patients taking nefazodone had less stage 1 sleep compared to patients taking fluoxetine. Our results are similar to this trial's findings except that the differences in this data at 8 weeks are less marked. Only the number of awakenings and amount of stage 1 sleep were higher at this stage in the paroxetine group than the nefazodone group and the

sleep onset latency in the nefazodone group was shorter. One explanation for this observation is that paroxetine has a less disturbing effect than fluoxetine on sleep in longer term treatment.

The results above, that of Rush (1998)[37] and previous work on depressed patients [119] and healthy volunteers [38 40] have shown similar effects of nefazodone on REM sleep, i.e. that nefazodone does not suppress REM sleep or increase REM latency. Rush 1998 showed nefazodone increased REM sleep compared to fluoxetine. Table 2.5 shows a summary of the effects of nefazodone on sleep architecture in published work.

	Normals	Normals	Normals	Normals	Depression	Depression	Depression
	1992 Sharpley open	1994 Ware open	1996 Sharpley parox/nef/ placebo	1998 Vogel nef/placebo	1994 Armatage open	1998 Rush nef/fluox	2002 Hicks nef/parox
TST	+			=		=	+
Sleep eff						+	+
SOL						=	=
No awakes					-	-	=
ROL	=	=	=	=	=	=	=
1					-	+	=
2					+	=	=
3						=	=
4						=	=
REM sleep	+	+	=	=	=	+	=
WASO	-				-	=	-

Key + increase

- decrease

= no change

Table 2.5 Published studies of the effects of nefazodone compared to placebo. fluoxetine or paroxetine on sleep architecture in normal or depressed patients.

How does nefazodone work to improve depression and promoting sleep? It has weak antagonist activity at alpha one adrenoreceptors which could lead to the increase in REM sleep in some of the reported studies above, but its alpha antagonist receptor properties are weaker than trazodone's which decreases REM sleep. mCPP, one of nefazodone's metabolite also decreases REM sleep. Nefazodone's weak alpha one antagonist receptor blocking properties may account for its role in improving sleep continuity, and its role in decreasing awakenings could be that its 5HT reuptake blocking effects are compensated by its 5HT2A/2C receptor agonist activity. However, nefazodone's role in not suppressing REM sleep like most antidepressants remains unexplained.

Subjective sleep quality and depth of sleep was increased in patients taking nefazodone early in treatment. This difference then decreased as treatment progressed and was not statistically significant at 8 weeks. There may be some sleep promoting effect of nefazodone, or the SSRI's sleep disturbing effect may be diminished as neuro-adaptive changes take place in the brain as the patient takes it for longer. Also as patients depression improves their reporting of clinical complaints may decrease despite continuing objective sleep disruption.[121]

Nefazodone has been shown in this trial and that of the multi-centered trial of Rush to improve TST, sleep efficiency and decrease number of awakenings compared to the SSRIs, fluoxetine and paroxetine. A newly presenting depressed patient may therefore benefit from commencing nefazodone rather

than fluoxetine or paroxetine if sleep complaints are a prominent symptom. The beneficial effects of nefazodone compared to paroxetine at only day 3 of treatment are evident in these results for TST and sleep efficiency which could help alleviate symptoms quickly in a sleep deprived depressed patient. One of the limitations of this study however is that there was no control group although the two drugs were directly compared against each other.

Since 2003 nefazodone has only been available on a named-patient basis in the UK. It has been associated rarely with hepatotoxicity. The incidence of death from liver failure under nefazodone is reported to be 1 in 250,000 to 300,000 patient years of treatment, which is greater than the general population. This has therefore resulted in a switch to the prescribing of trazodone, nefazodone's sister drug which has shown sedative effects in depression[129] but may have more problem with side effects, which include sedation, dizziness and psychomotor impairment and priapism. The incidence of priapism is between 1 in 1000 and 1in 10,000 [130] and has been shown to occur more frequently with trazodone than nefazodone.[40]

Chapter 3

Does Nefazodone improve sleep in primary insomnia? A presentation of objective and subjective data.

This second study describes a cross over trial that investigates whether nefazodone compared to placebo has beneficial effects on sleep in patients with primary insomnia.

Nefazodone was not found, compared to placebo, to increase sleep efficiency, total sleep time or decrease number of awakenings in patients with primary insomnia.

My role was recruitment of patients performance of the EEG recordings at patients homes, visual correction of the PSG recordings after they had been scored by the computer, analysis of the results and write up for this chapter.

3.1 Introduction

The use of the more sedating antidepressants as treatment for insomnia has not been sufficiently supported by clinical trials. Some antidepressants are used in clinical practice to promote sleep in patients with insomnia but without signs and symptoms of clinical depression. However this practice is anecdotal and is not backed up by published research in the literature. There is only a small amount of evidence from randomized placebo controlled trials showing efficacy for doxepin[131] and trimipramine[132] and paroxetine[133] in patients with primary insomnia. The antidepressant trazodone is also used in primary insomnia. In open label studies beneficial effects of trazodone on the sleep in healthy young adults [134] have been shown but there have been no controlled

trials of its use in primary insomnia. This is perhaps surprising as it is now quite widely used for primary insomnia or insomnia secondary to depression. The considerable effects on sleep of antidepressants (see chapter one) can be demonstrated in healthy and depressed patients. The properties of antidepressants thought to improve sleep are:

(i) Antihistaminergic action e.g. sedating tricyclics such as triimipramine, trazodone (nefazodone has a weaker anti-histaminergic action), and mirtazapine

(ii) 5HT 2 receptor antagonism e.g.amitriptyline, nefazodone, trazodone, and mirtazapine

(iii) Inhibition of the alpha one adrenergic receptor e.g. trazodone (weaker action, nefazodone)

The use of nefazodone as a hypnotic in insomnia has also not been fully investigated. As discussed in chapter two, there have been two studies in normal volunteers in which nefazodone has caused an increase in REM sleep.[40] [42] However, these results were not confirmed by Vogel (1998).[118] In depressed patients nefazodone also exerts minimal effects on sleep continuity, as opposed to SSRIs, by increasing sleep efficiency, decreasing awake and movement time and decreasing number of awakenings or by not affecting these parameters.[37] [119] [128] These studies also found a possible increase in REM sleep and unaltered REM latencies in contrast to the clear REM sleep suppression and increased ROL under SSRI treatment.

There has been one open label study, in primary (psychophysiological) insomnia, investigating the effect of nefazodone on sleep in 32 patients.[135] Patients met the DSM 1V (1994) criteria for primary insomnia and simultaneously the ISCD (1997) criteria for psychophysiological insomnia, therefore denoting a form of chronic insomnia without underlying medical or psychiatric disease. Patients with depression were included if they scored over 15 on the Hamilton Anxiety and Depression (HAM-D). They underwent two baseline polysomnographs on consecutive nights, after fourteen days free from any medication with central nervous system action. The patients then took 100-400mg of nefazodone daily before bedtime (the dose was increased after 5 or 10 days depending on efficacy and tolerability of the drug.) After 27 and 28 days two further sleep recordings were performed. Subjective sleep measurements were assessed using the Pittsburgh Sleep Quality Index (PSQI) [136], and a " Morning Questionnaire" on the previous night's sleep.

Comparing night 2 and night 28 the polysomnographic data showed significant increases in SOL, stage 2 and REM sleep. Number of awakenings and stage one were significantly decreased. However, TST and sleep efficiency and REM onset latency were not significantly increased. There were however significant improvements in PSQI total scores and all subscales except for subscale 2 (sleep latency) improved significantly from baseline to night 28 under treatment.

The trial described in this chapter had a crossover design comparing nefazodone 100mg daily taken before bedtime with placebo in 10 patients to investigate whether nefazodone was associated with any objective or subjective improvement on the sleep of patients with primary insomnia after two weeks.

3.2 Method

Patients

Patients were selected who were aged between 18 and 65 years, who met the diagnostic criteria for primary insomnia (International Classification of Sleep Disorders 2001) and who had no current history of depression. Patients were excluded if they were taking other psychotropic medications, were allergic to nefazodone, had current or past mental illness within the last year, or who had current substance abuse problems.

This was a double blind crossover study to look at the effects of nefazodone on sleep in primary insomnia. Patients were given a two week washout from any psychotropic medication. Ten patients were randomized to start nefazodone or placebo for two weeks. After a two-week washout period, they crossed over to either nefazodone or placebo for a further two weeks of treatment.

Objective sleep measurement

At the end of each of the two-week treatment periods overnight sleep was measured at home by polysomnography. The Medilog 9000-2 system was used to measure the EEG using the montage (C4-A1, C3-O1). The methodology for

collecting objective sleep data mirrored exactly that used in the nefazodone and paroxetine in depression study described in Chapter 2. The main outcome variables were the objective sleep parameters (Sleep Efficiency, TST, and number of awakenings) as in Chapter 2. Other sleep parameters were also measured. Automatic scoring with visual correction (by JAH) was also applied as in chapter 2.

Subjective sleep measurements

The following subjective sleep measures were used:

1. St Mary's Sleep Questionnaire (Please see appendix for copy)

2. Leeds Sleep Questionnaire (Please see appendix for copy)

Both questionnaires were completed on the morning after each objective sleep measurement.

3. Sleep diaries were also completed for each night of the treatment periods. Each subject had by the end of the study completed a sleep diary for 2 weeks while on medication and for 2 weeks while on placebo.

Determination of sample size

If objective and subjective sleep measures are compared between each treatment period using paired t tests, a sample size of 10 patients has 92% power at the 5% significance level to detect a 10% difference in mean total sleep time between drugs.

3.3 Statistical Analysis

Paired t tests or Wilcoxon Sign Rank tests were performed to compare the objective data and subjective data when the patients were on nefazodone compared to placebo.

3.4 Results

Objective Results

All sleep parameters except SOL, ROL, WASO and Number of awakenings were normally distributed. A paired t test was carried out on the normally distributed data (see Table 3.1) and a Wilcoxon Sign Rank on the non-normally distributed data (see Table 3.2). Data shown here is for TST, Sleep efficiency, and number of awakenings. (The other objective sleep parameter data is available in the appendix 3.) Figures 3.1, 3.2, and 3.4 graphically portray in bar charts the primary outcome varaiables, Total sleep time (TST), Sleep efficiency, and Number of awakenings on nefazadone versus placebo. (Figure 3.3 of SOL is in appendix 3.) Patient 6's placebo recording was not analyzed due to poor tape quality. It should be noted that all sleep efficiencies were above 60% and the majority of sleep efficiencies were above 80%. There was no significant change in any sleep parameters comparing nefazodone treatment with placebo.

Sleep Parameter	Nefazodone (Mean value for whole group) n=10	Placebo (Mean value for whole group) n=10	Mean Difference	Standard Deviation	t statistic (paired t test)	P value
TST (min)	405.7	390.3	-15.4	74.8	-15.4	ns
Sleep Efficiency(%)	85.9	82.7	-3.2	9.0	-3.2	ns

Slp eff = sleep efficiency SOL =sleep onset latency ROL= REM onset latency

SD =standard deviation of the difference df = degrees of freedom ns = non-significant

Table 3.1: Paired t test Results

	Nefazodone (Mean value for whole group) n=10	Placebo (Mean value for whole group) n=9 except for SOL when n=10	Z value	P value
Number of Awakenings	14.8	15.1	0.3	ns

Table 3.2: Wilcoxon Sign Rank Test Results

Figure 3.1:Total Sleep Time for Nefazodone versus Placebo patients 1-10

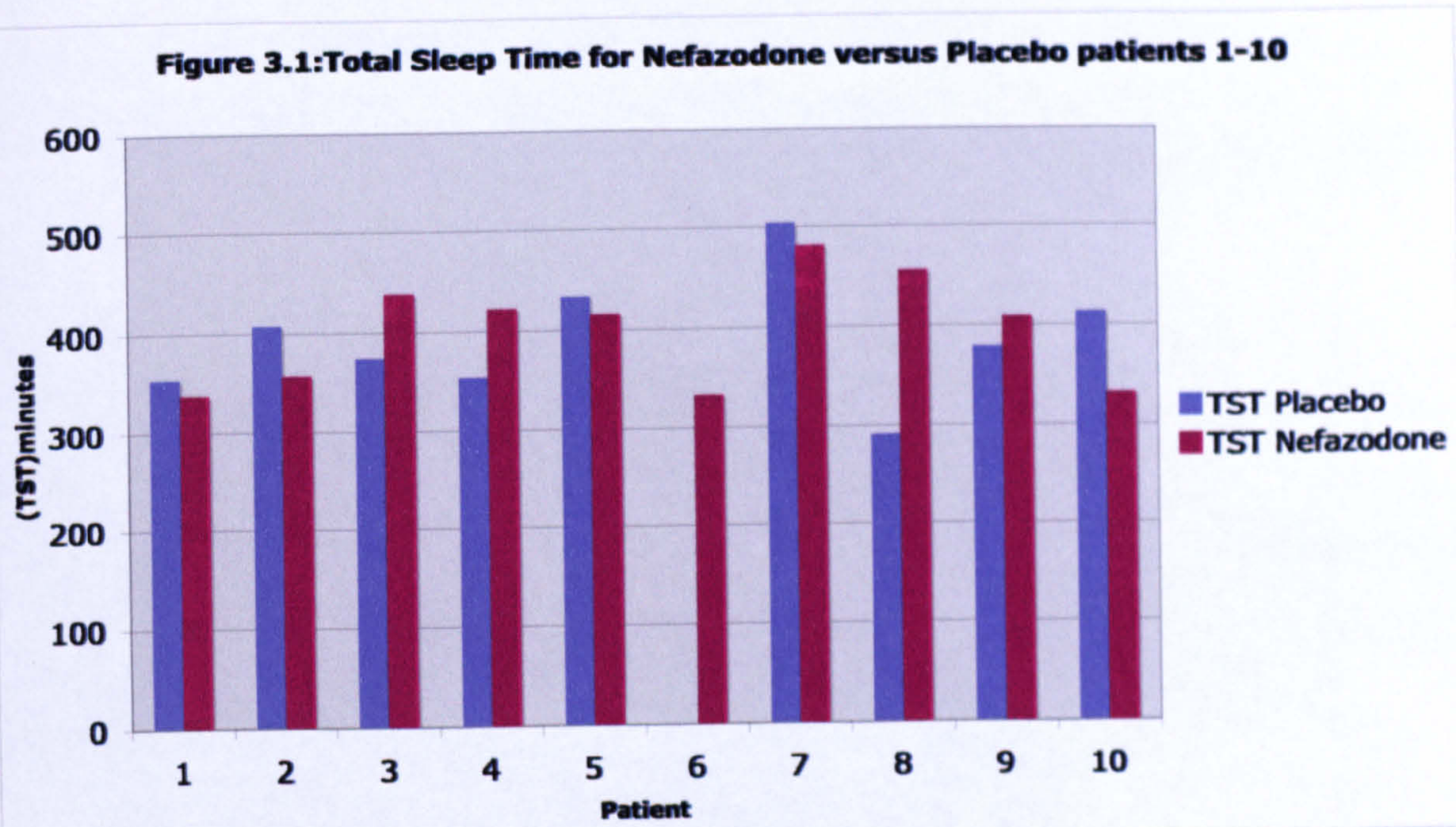


Figure 3.2: Sleep Efficiency Nefazodone versus Placebo Patients 1-10

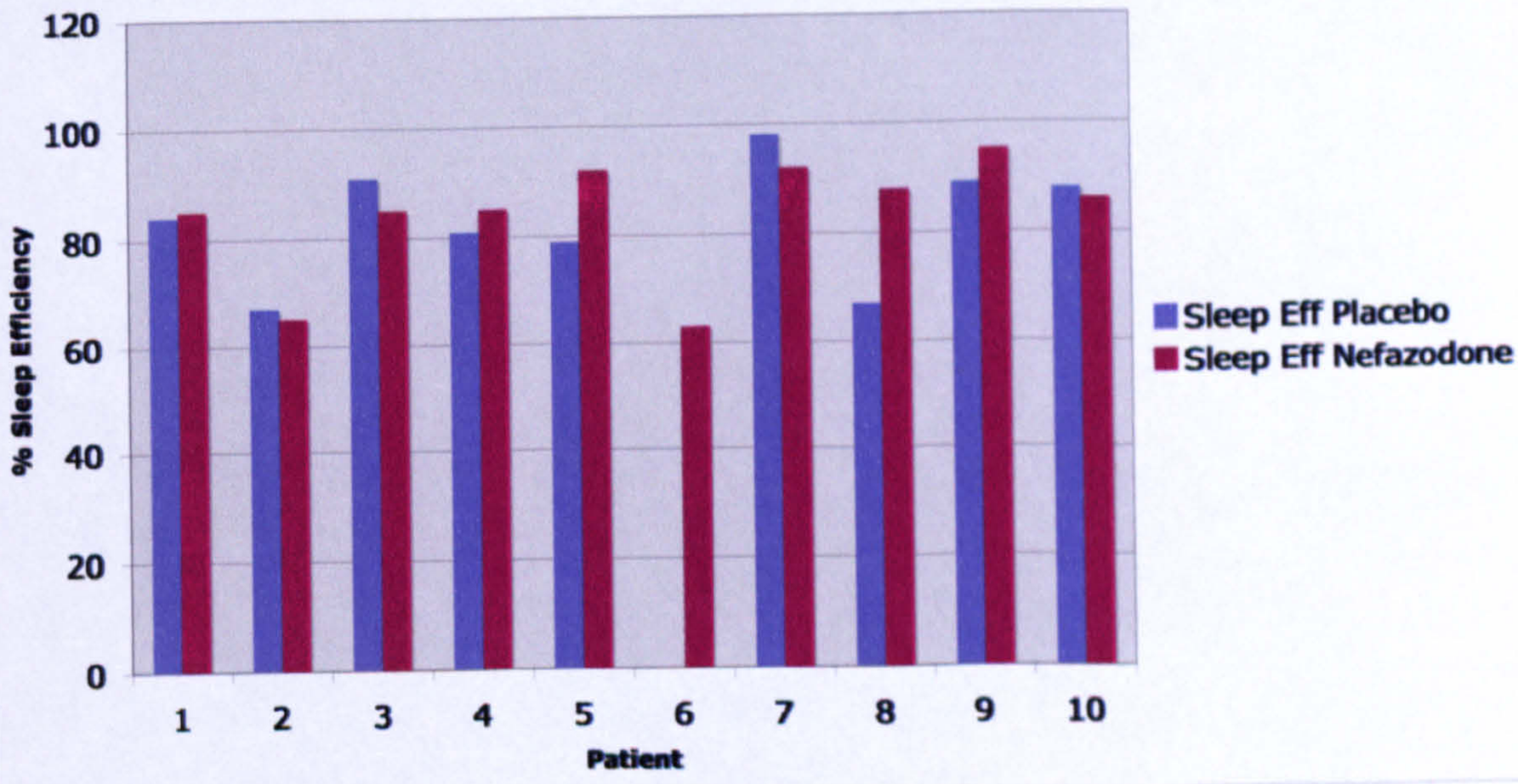
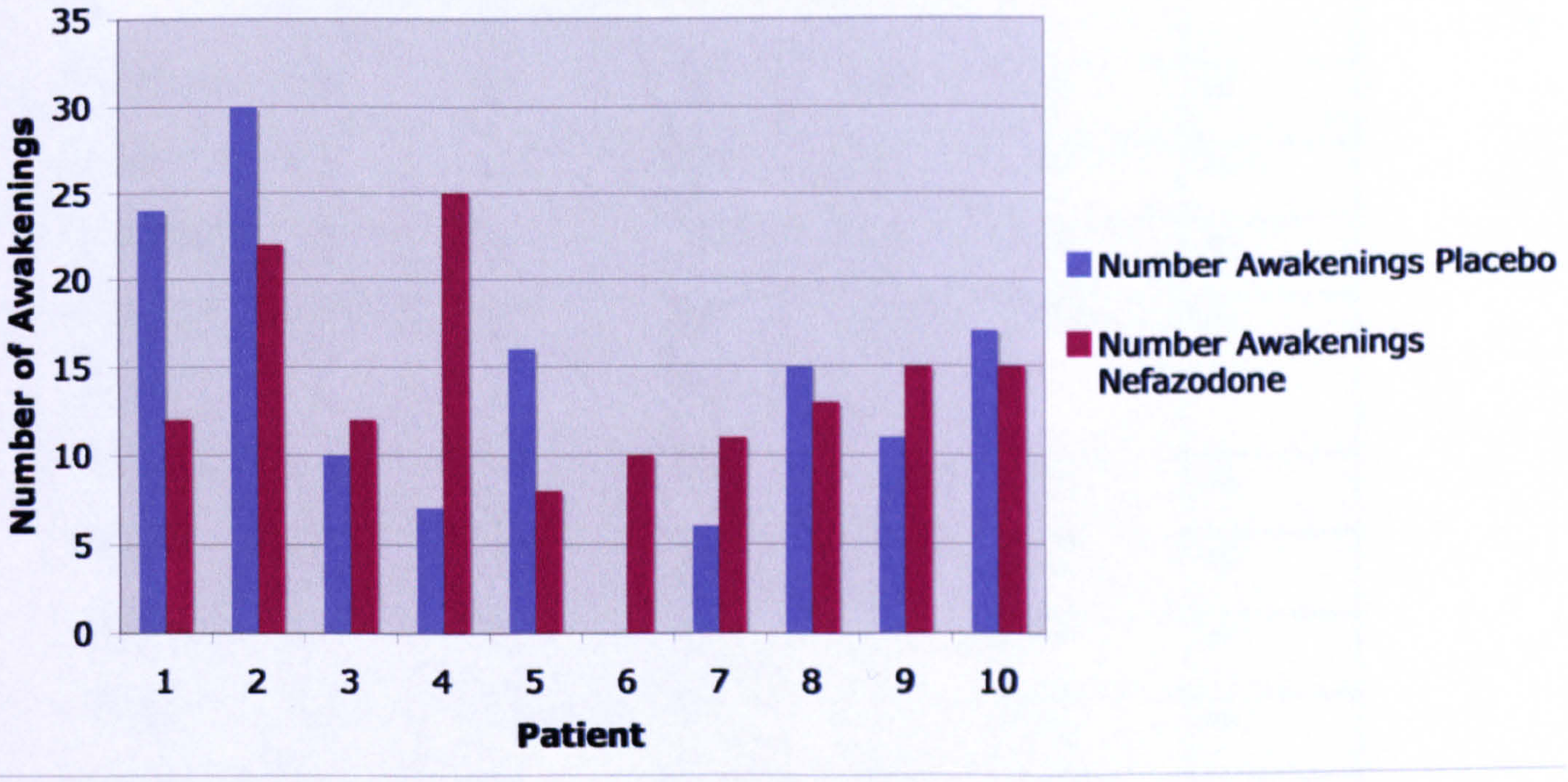


Figure 3.4: Number of Awakenings Nefazodone versus Placebo Patients 1-10



Subjective results:

Table 3.3 tabulates the results and statistical analysis of the St Mary's Hospital Questionnaire. Figure 3.8 shows "how well you slept data." (Please see appendix 3 for other graphs of SMHQ data, Figures 3.5-7) but there were no significant differences for any of the SMHQ Questionnaire scores when comparing nefazodone and placebo.

	Nefazodone (Mean value for whole group)n=10	Placebo (Mean value for whole group)n=10	Mean Difference	S D	t statistic	p value
SOL (mins)	-48	74	26	93.4	0.9	ns
Depth	4.0	3.7	-0.3	2.1	0.7	ns
Awakenings	2.6	2.9	-0.3	1.9	0.6	ns
How much (mins)	281.5	294	12.5	135.2	42.8	ns
How well	3.1	3.5	0.4	1.4	0.5	ns
Clear	-3.5	3.6	0.1	1.0	0.3	ns
Satisfied	-2.5	3.2	0.7	1.7	0.5	ns
Difficult	-1.8	1.9	0.1	1.3	0.4	ns
How long to sleep (mins)	-54.5	91	36.5	91.0	29.0	ns

Table 3.3: Results of St Mary's Hospital Questionnaire

Figure 3.8: 'How well you slept' SMHQ Nefazodone versus Placebo

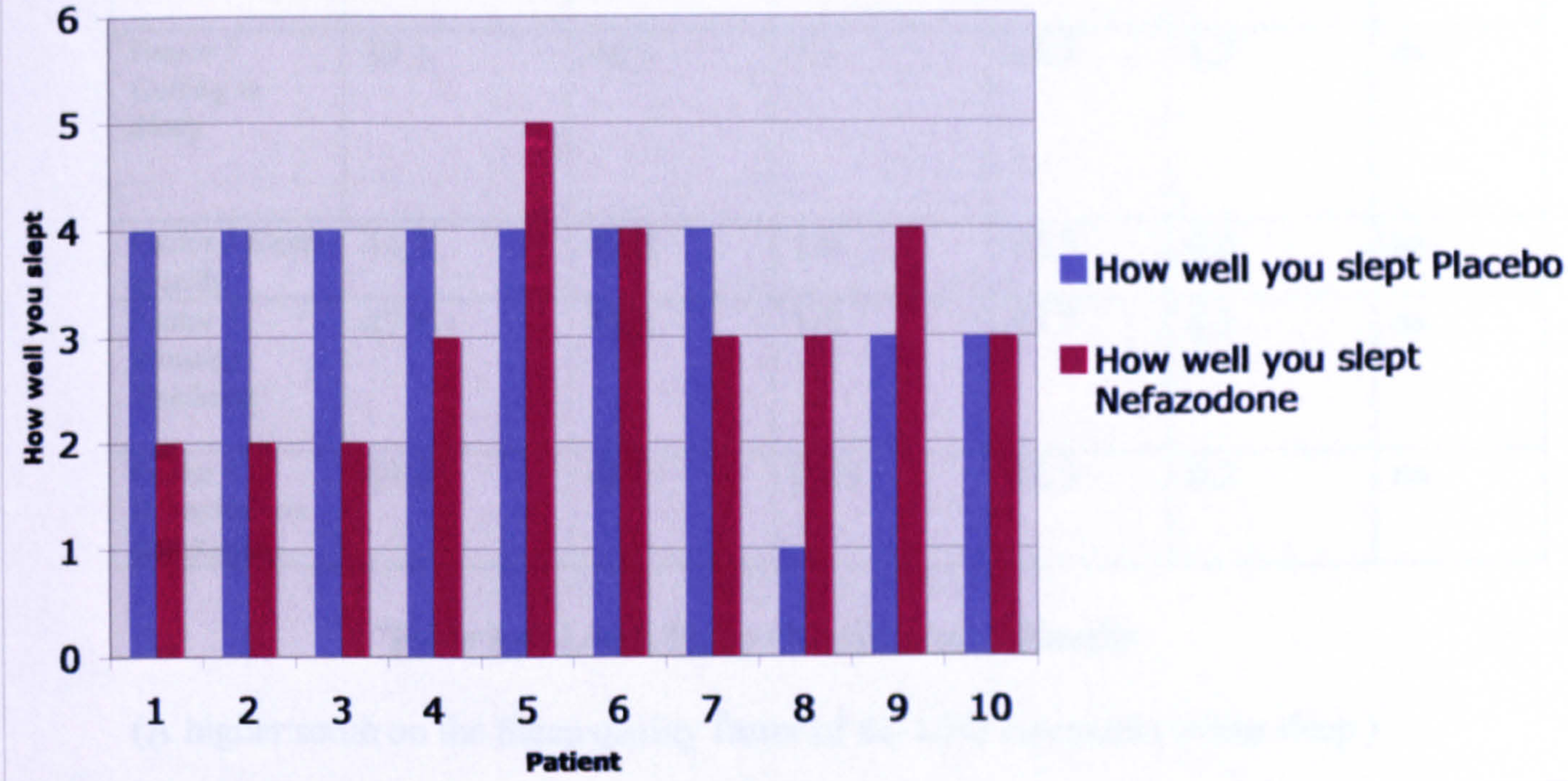


Table 3.4 tabulates the results and statistical analysis of the Leeds Sleep Questionnaire. Figures 3.9 to 3.12, (please see appendix 3,) graphically present the results for the subjective sleep variables "Getting to sleep", "Sleep Quality", "Morning Tiredness" and "Behaviour on Awakening". There were no significant differences for any of the Leeds Sleep Questionnaire scores when comparing nefazodone and placebo. Note that Patient 8 did not complete the Leeds sleep questionnaire on the placebo night.

Factor	Nefazodone (Mean value for whole group) n=9	Placebo (Mean value for whole group) n=10	Mean Difference	S D	t statistic	p value
Factor 1 Getting to Sleep	39.1	46.3	7.1	14.3	1.3	ns
Factor 2 Sleep Quality	44.7	42.8	1.9	22.9	0.3	ns
Factor 3 Morning Tiredness	47.8	46.8	1.0	23.7	0.1	ns
Factor 4 Behaviour on Awakening	49.6	48.7	0.89	12.3	0.2	ns

Table 3.4: Leeds Sleep Questionnaire Results

(A higher score on the Sleep quality factor of the LSQ represents worse sleep.)

Sleep Diaries

Sleep Diaries were completed for the 14 days of treatment with nefazodone or placebo. Table 3.5 tabulates the statistical analysis and results of sleep diary data. The three variables, "Sleep Onset Latency", "Total Sleep Time", and "Sleep Quality" were analyzed. There were no statistically significant differences between results for nefazodone and placebo. Figures 3.13-3.15 graphically depict the same data.

	Mean Nefazodone day 1-14	Mean Placebo day 1-14	Mean Difference	S D	t statistic	p value
SOL (mins)	93.7	86.7	-7.0	60.7	-0.4	ns
TST (mins)	289.8	305	15.2	36.0	1.3	ns
Sleep quality	4.7	4.9	0.2	1.1	0.4	ns

Table 3.5: Sleep Diary Data

Figure 3.13: Sleep Diary (means day1-14) Sleep Onset Latency (SOL) Nefazodone versus Placebo

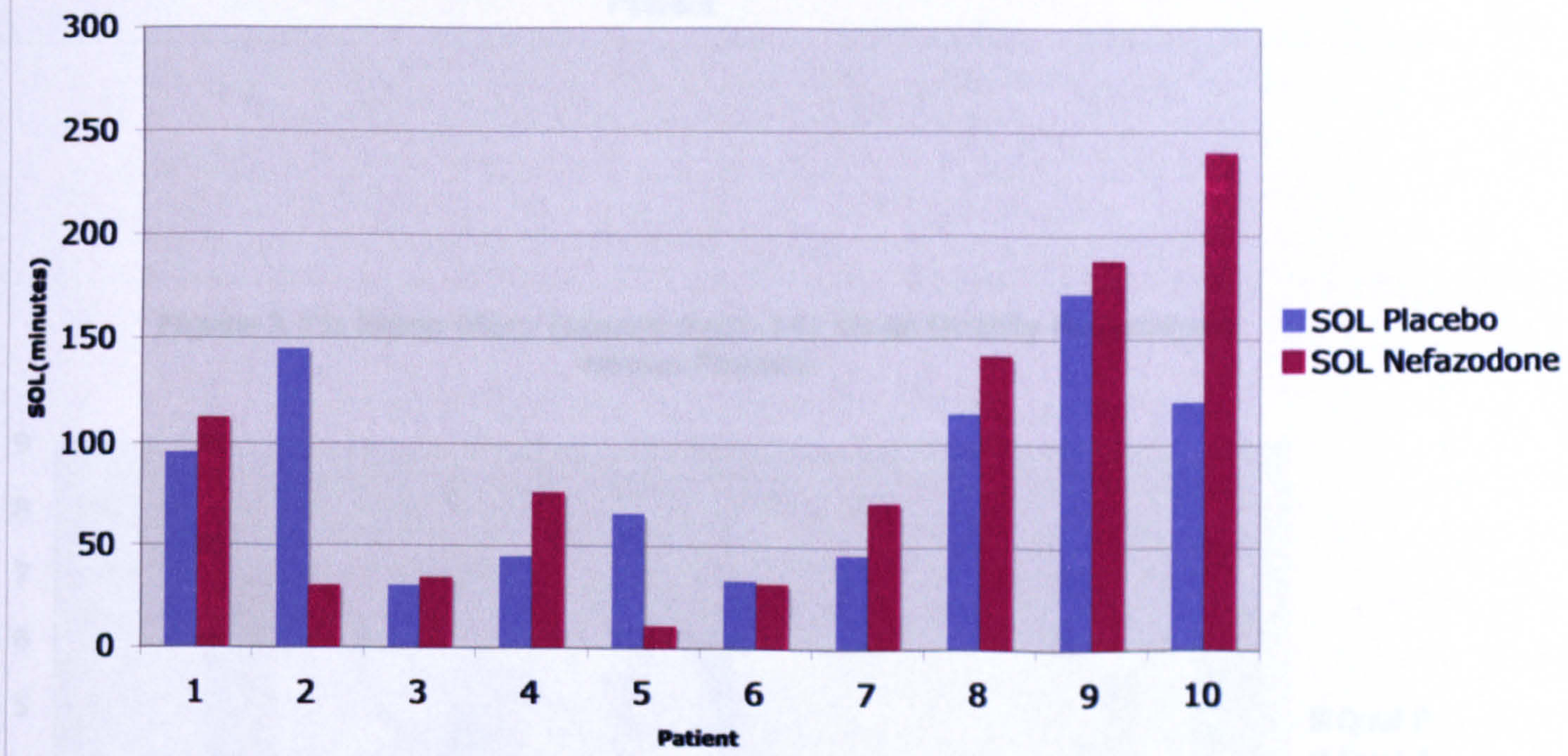


Figure 3.14: Sleep Diary (means day 1-14) Total Sleep Time(TST) Nefazodone versus Placebo

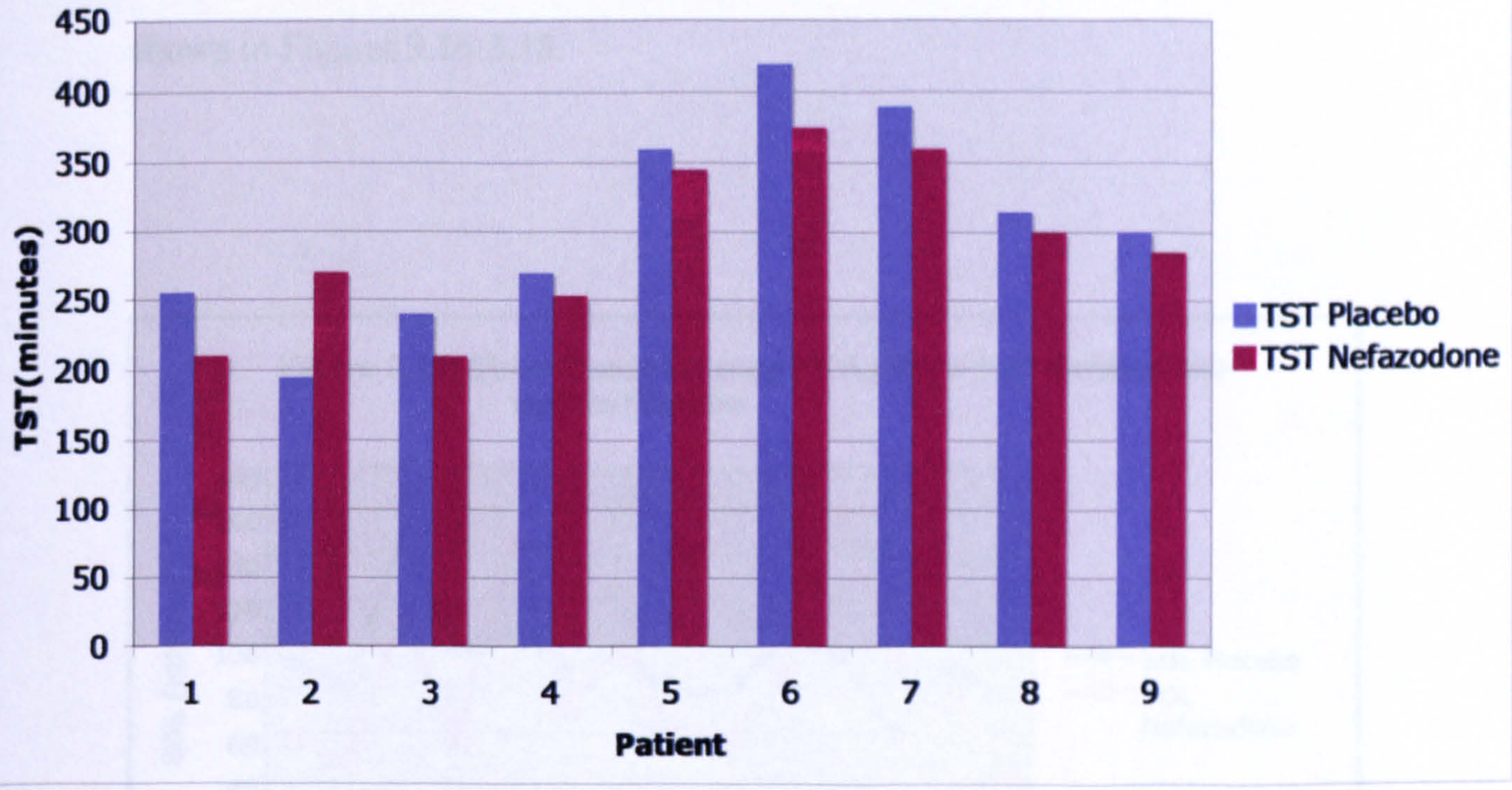
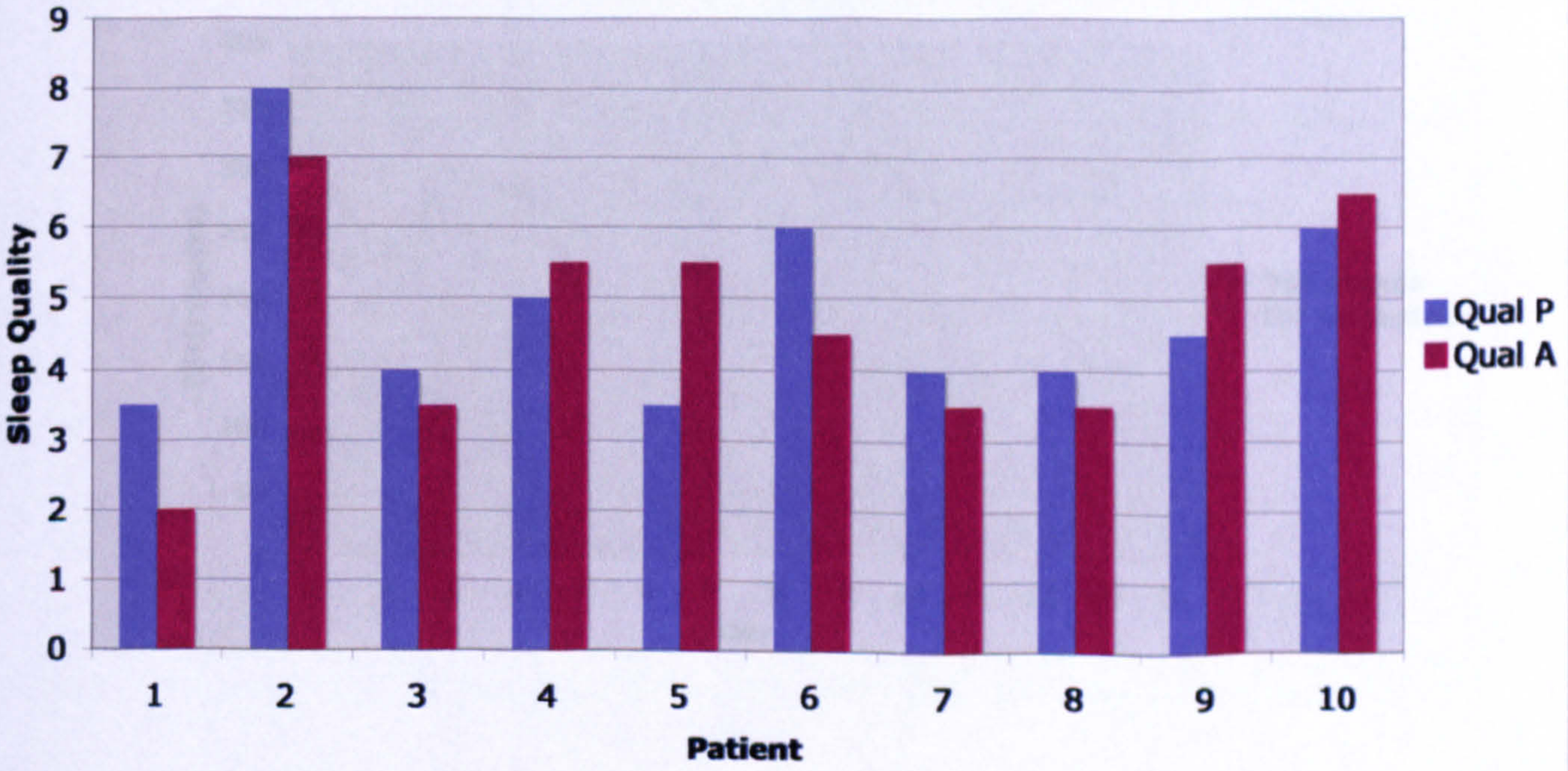
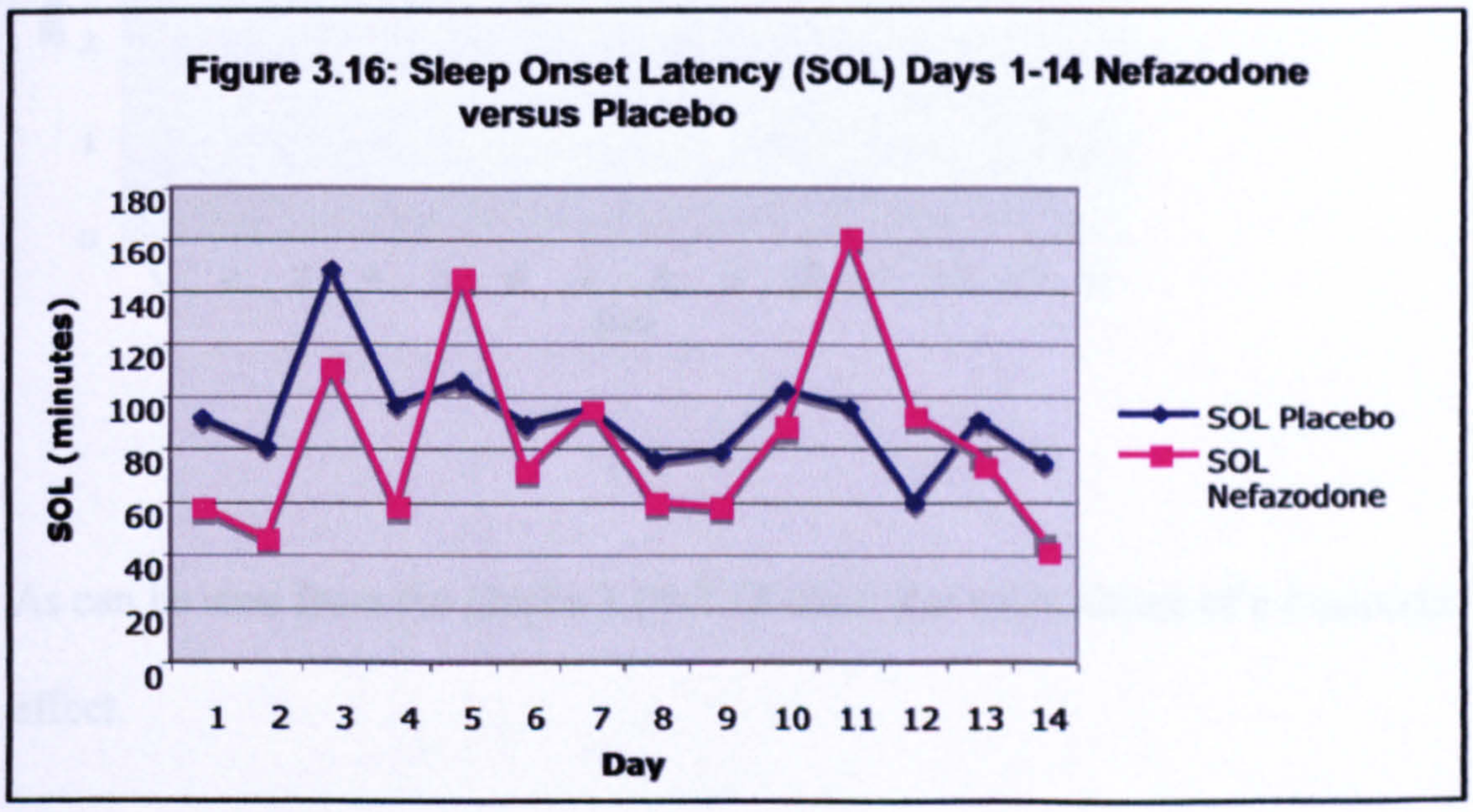


Figure 3.15: Sleep Diary (means day1-14) Sleep Quality Nefazodone versus Placebo



Treatment effect Day 1-14

In order to establish if there was a treatment effect from day 1-14 of nefazodone the means of SOL, TST, and sleep quality were plotted and are shown in Figures 3.16-3.18.



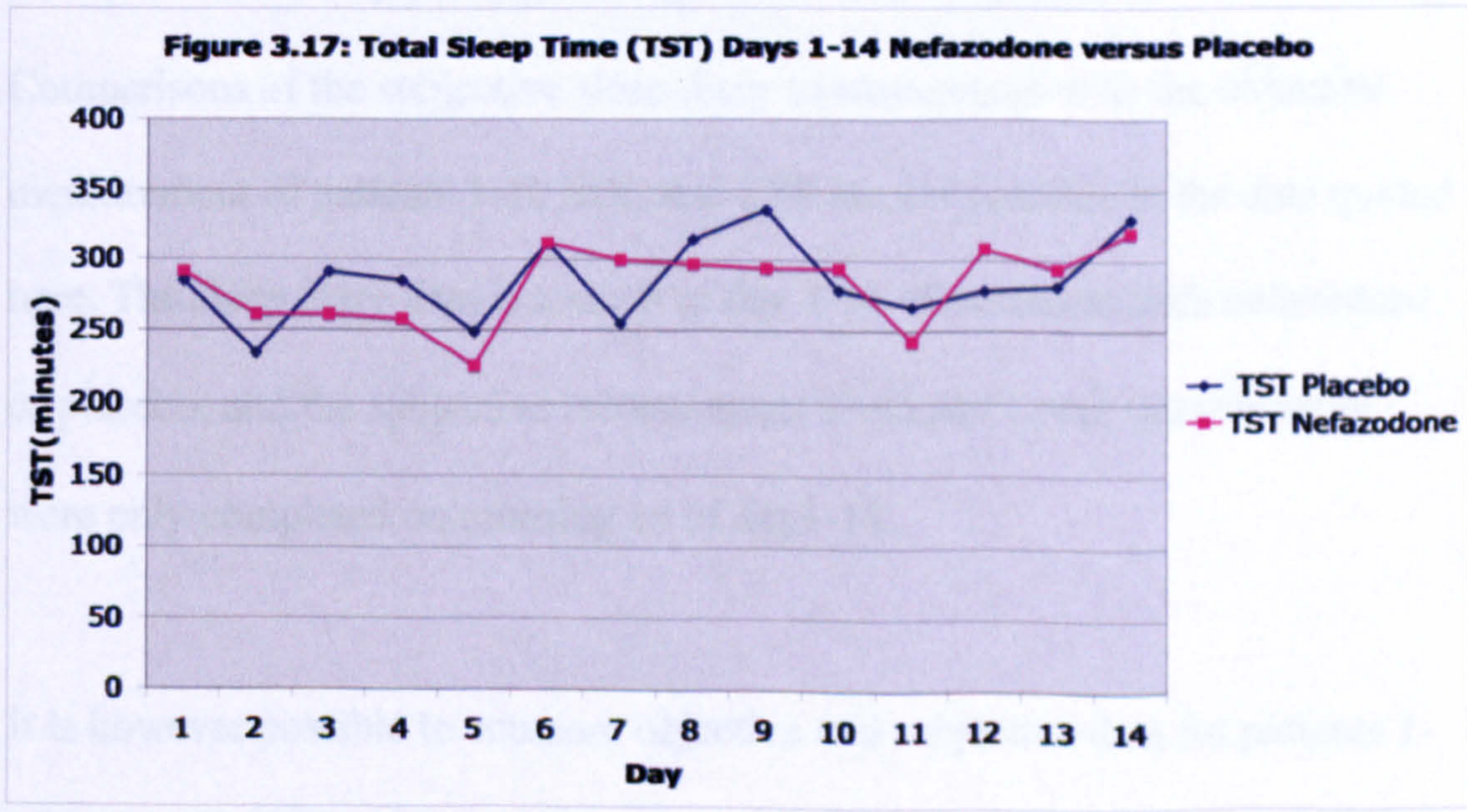
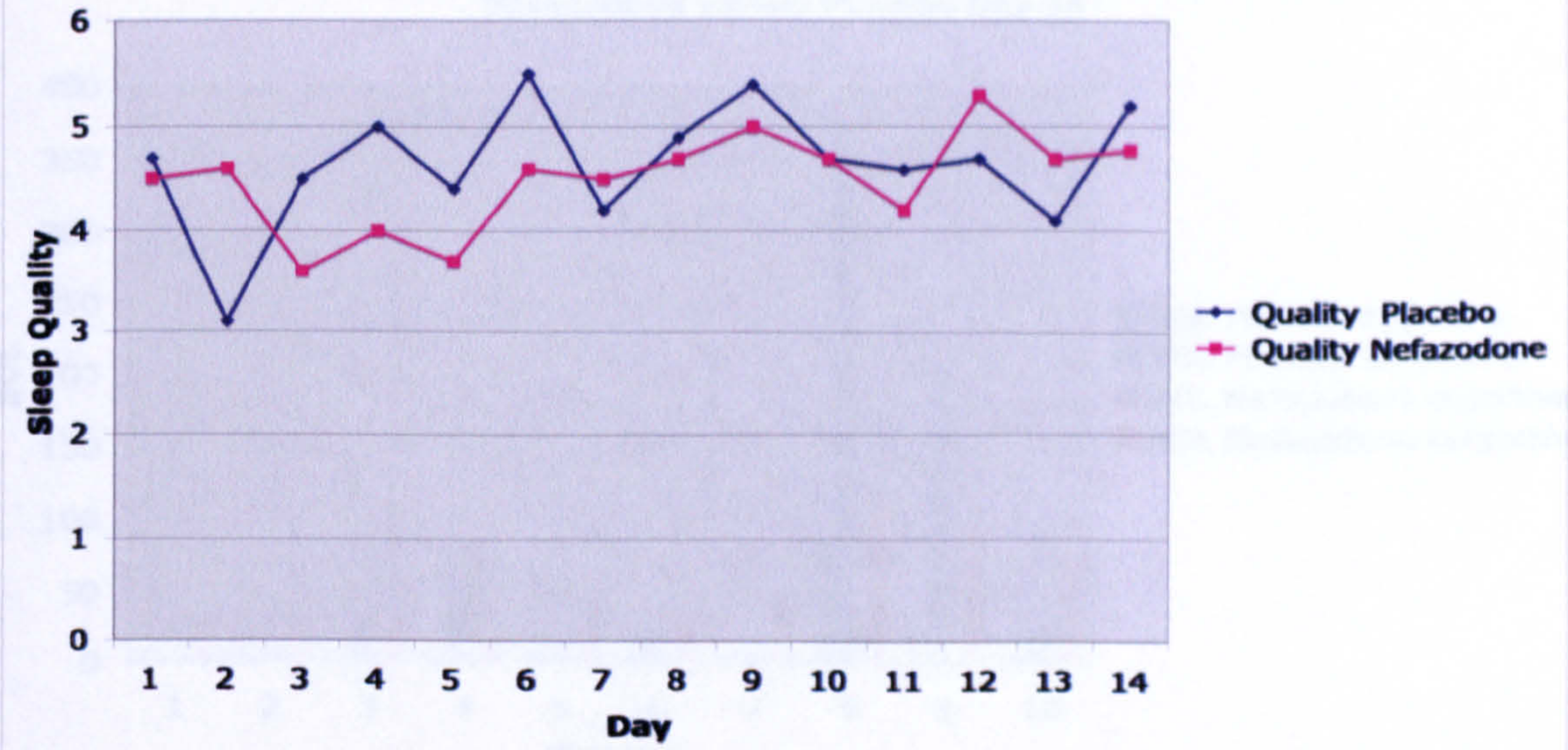


Figure 3.18: Sleep Quality Days 1-14 Placebo vs Nefazadone



As can be seen from the graphs 3.16-3.18 there was no evidence of a treatment effect.

Comparison of Objective and Subjective Sleep Nefazodone versus Placebo

Comparisons of the subjective sleep diary measurements with the objective measurement of patients 1-10 SOL and TST are not possible in the data quoted here. The sleep diary data is a mean of day 1-14 of treatment with nefazodone or placebo, and the subjective measurement SMQ and Leeds questionnaire were only completed on morning 14 of day1-14.

It is however possible to compare objective and subjective data for patients 1-10, using SMHQ subjective SOL, subjective TST and subjective number of awakenings as all data refers to night 14 of placebo or nefazodone. See Figures 3.19 – 3.21:

Figure 3.19: Comparison of objective PSG and subjective SMHQ SOL Nefazodone versus Placebo Day 14

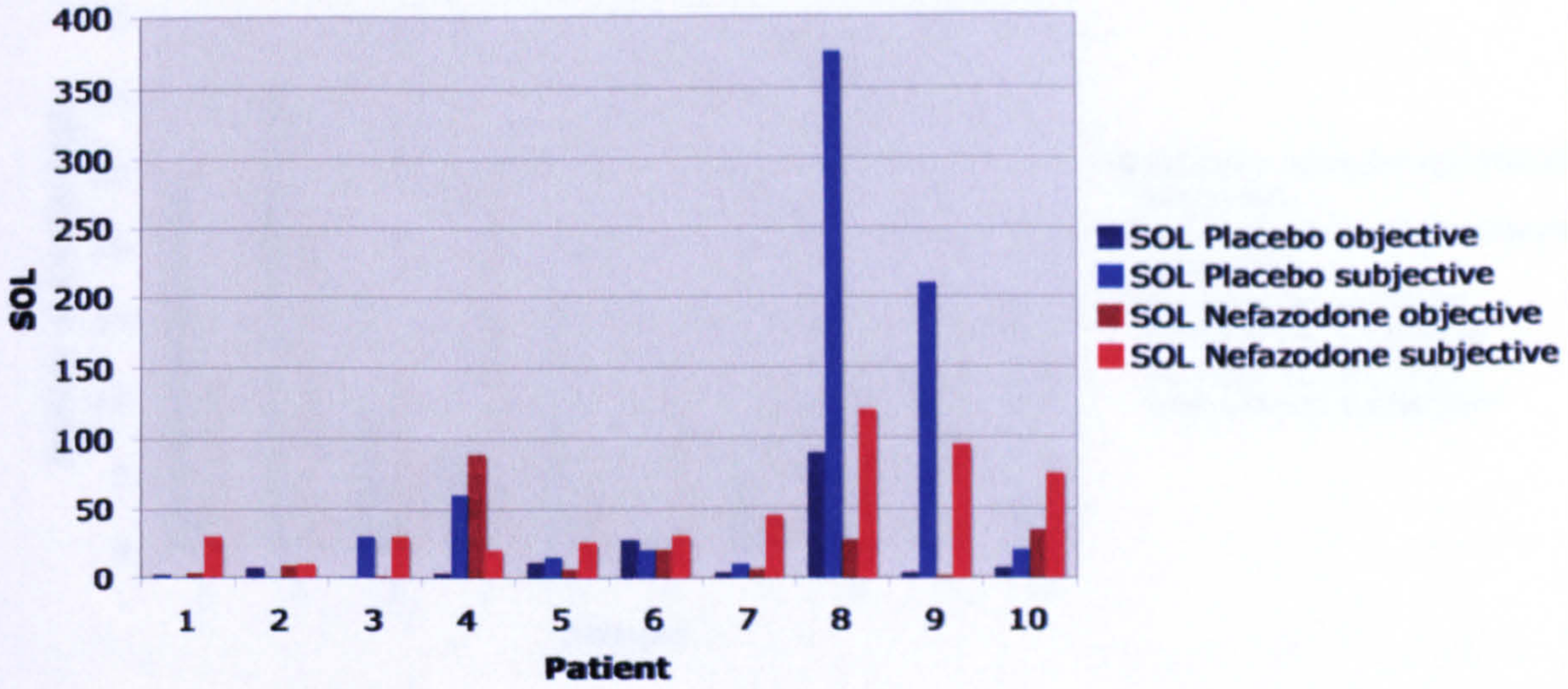


Figure 3.20: Comparison of objective PSG and subjective Total Sleep Time/"How much Sleep" SMHQ Nefazodone versus Placebo Day 14

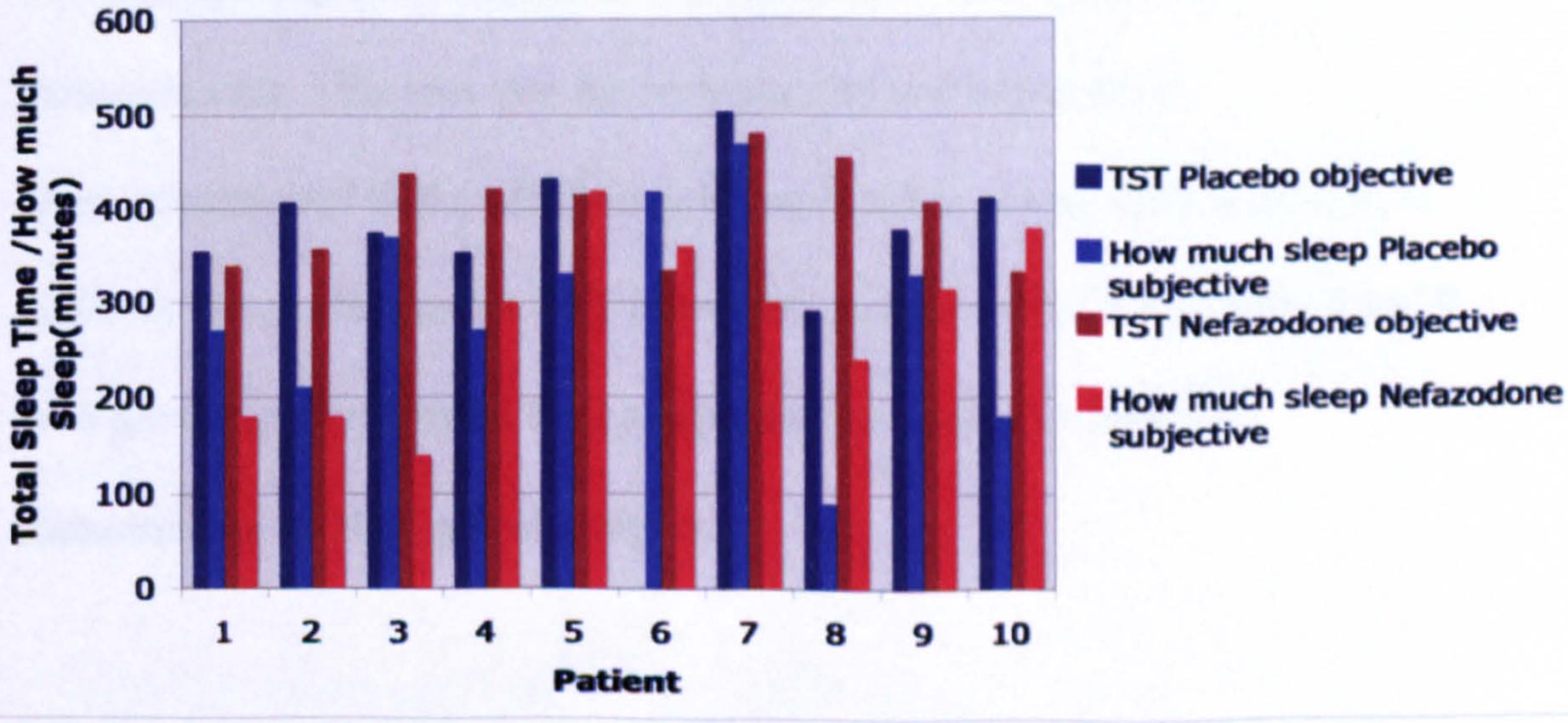
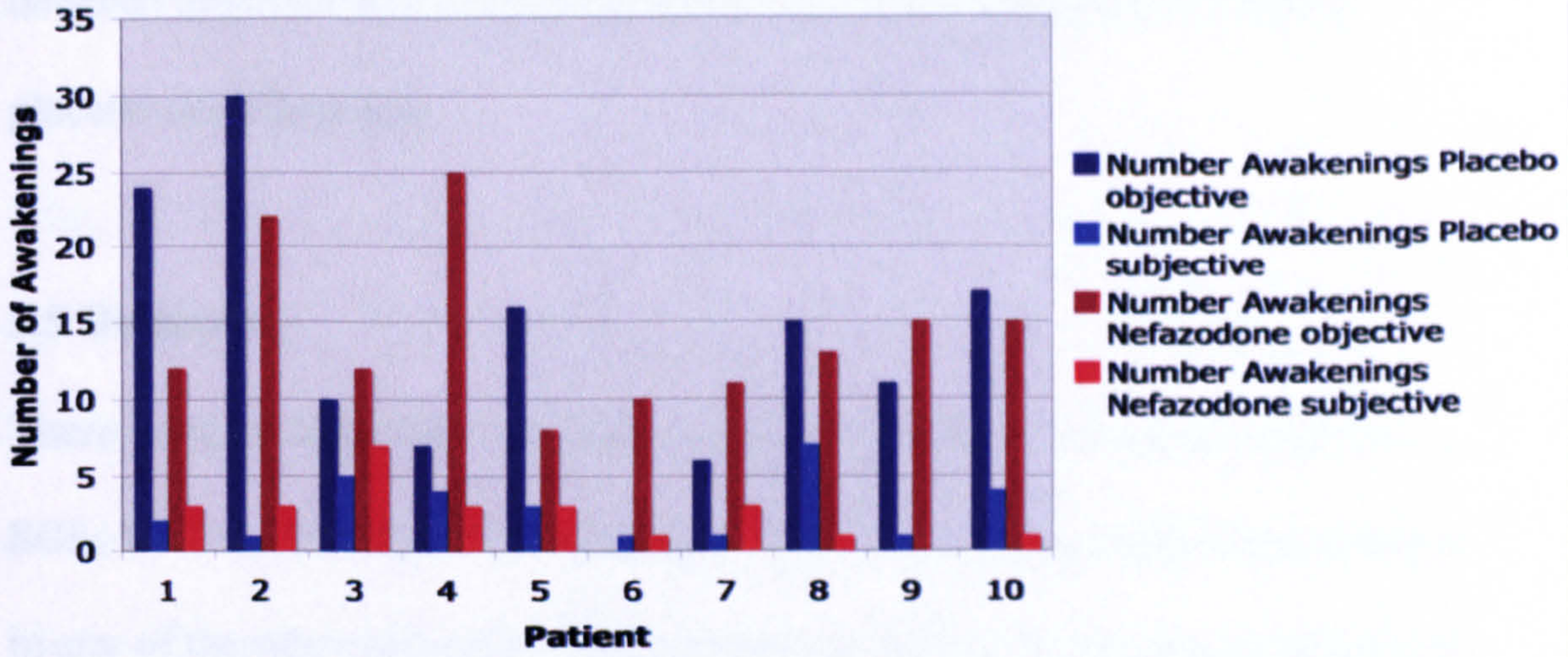


Figure 3.21: Comparison of objective PSG versus subjective SMHQ Number of Awakenings Nefazodone versus Placebo Day 14



Nearly all patients underestimated "How much Sleep" they got subjectively when comparing their subjective SMHQ scores with objective TST measurements. This was true for both placebo and nefazodone.

Overestimation of SOL, which may be expected in people with insomnia, is however not as clear as for TST from these results except for patients 8 and 9 who greatly overestimated their sleep onset compared to objective measurement on their placebo nights.

Number of Awakenings would be expected to be higher for both nefazodone and placebo when measured objectively by EEG. This is because patients will not be aware of every arousal, if it is brief, even though it is scored on an EEG as an awakening. Therefore it is difficult to compare objective and subjective

data for number of awakenings, however there was no significant difference between number of awakenings on objective and subjective measurements between nefazodone and placebo. There was also no significant correlation between objective and subjective awakenings when patients were taking placebo or nefazodone.

3.5 Discussion

There were no significant changes in the main objective outcome variables SOL, TST and Number of awakenings. There were also no significant changes in any of the other objective sleep parameters. Patient 2 complained bitterly of poor TST and quality sleep. This would seem to be supported by the objective data showing a sleep efficiency of around 60%. However, he may have had a lower sleep efficiency due to spending more Time in Bed but not actually sleeping and his TST was unremarkable compared to the rest of the patients. In fact Patient 2's Time in Bed results were the highest of the patients recorded at over 600 minutes for placebo night and over 550 minutes for nefazodone. Patient 6 also has a lower sleep efficiency than the rest of the patients, (there are no recordings for patient 6 on nefazodone as this tape had technical problems) however, Time in Bed for patient 6 was also high: 531 minutes (nefazodone) and 563 minutes (placebo).

In this study nefazodone has also not made any subjective improvements in sleep as measured by three separate subjective measures: SMQ, Leeds, and fourteen-day sleep diary. These objective and subjective results are in contrast to Wiegand et al who demonstrated significant increases in SOL, stage 2 sleep

and REM sleep.[135] However they found TST, sleep efficiency and REM sleep onset latency were not significantly increased. In Wiegand's study, the number of awakenings, stage one sleep and SWS were significantly decreased; they therefore showed that nefazodone's effect in primary insomnia might be on sleep continuity.

Wiegand, however, found more pronounced subjective changes in sleep than objective changes. Pittsburgh Sleep Questionnaire Index (PSQI) scores,[136] decreased and all subscores decreased except for sleep latency after four weeks administration of nefazodone. The subjective improvement described by Wiegand could be related to the antidepressant action of the drug despite the exclusion of clinically relevant depression. Nowell et al.[133] looked at paroxetine in a small study in primary insomnia (n-=14). There were no objective improvements on PSG, but eleven patients decreased PSQI scores.

Trimipramine may have some sleep promoting properties in insomnia. It has been compared in a double blind placebo and lormetazepam-controlled study in patients in primary insomnia.[132] Objective PSG measurements showed increased sleep efficiency but not increased TST, of subjects taking trimipramine compared to placebo. Lormetazepam decreased wake time compared to placebo. Trimipramine and lormetazepam had significant effects on decreasing overall PSQI scores compared to placebo. On some items of the PSQI, trimipramine demonstrated better results than lormetazepam.

Doxepin has also been investigated in a 4-week placebo controlled trial (n=47) in patients with primary insomnia. Objective measurements showed increased

sleep efficiency. Subjective sleep quality, daytime performance and energy were also assessed and statistically significant improvements in sleep quality were found [131].

However all these studies are with relatively small numbers with some high drop out rates and also raise questions as to whether statistically significant changes are clinically significant to the patient.

The limitations to this study are also small patient numbers, and that patients recruited in this study with insomnia do have sleep misperception (SMP) i.e. they sleep better when measured objectively than they perceive subjectively.

SMP may mean the patients in this study were less severe "insomniacs" than they perceive or we anticipated, as when measured objectively, the majority had sleep efficiencies of 80% and above. Consequently the measurable effects of any sleep promoting medication may have been less marked. Objective and subjective measurements of total sleep time was underestimated by most of this group of insomnia patients by approximately 100 minutes, which shows a large SMP. Interestingly SOL was not overestimated by the majority of patients by such an amount or as consistently.

How often does sleep misperception occur? The underestimation of total sleep time and overestimation of sleep latency and number of awakenings in primary insomnia has been said to be 25-50% [137], but it also occurs in insomnia associated with depression.[99] The patients in this study most of who have had primary insomnia for many years probably have SMP. They could be helped further by the work of Tang and Harvey[138 139], (see chapter one and five). Tang

and Harvey have investigated verbal and behavioural techniques to feedback objective and subjective differences between people with insomnia's actigraphic and sleep diary recordings. They have shown that this can help correct SMP for the following night's sleep.

In this study, using 100mg of nefazodone, there were no reported side effects. However Wiegand who used 100-400mg of nefazodone (with the majority taking 200-400mg by day 28) had 11 dropouts from 31 patients due to side effects that included predominantly nausea, vertigo and a dry mouth. Interestingly the majority of dropouts occurred at doses of 100mg or 200mg and between days 3-15 of the study. Wiegand recommended a lower dose range in order to achieve better tolerability of the drug. It should be noted that he used doses recommended for the treatment of depression. Other antidepressants that have been used for insomnia rather than depression have an effect at lower doses e.g. doxepin.[131] However in this small study 200mg/day may have produced more biological and clinical effects without side effects. Perhaps the insomnia relieving effects of nefazodone reported in the other studies above is exclusively caused by its blocking action on 5HT2 receptors that is independent from its antidepressant effect.

Since 2003 nefazodone has only been available on a named-patient basis in the UK, see chapter two This has led to nefazodone's sister drug trazodone (which is used widely in the USA,) and now more commonly in the UK, being used to treat depression with associated insomnia and occasionally used to treat primary insomnia. As mentioned above it has been shown to promote sleep in

healthy controls,[134] in depression,[129] and in open studies in primary insomnia. A double blind placebo controlled trial of trazodone in primary insomnia and/or depression with secondary insomnia is now required to establish its efficacy in primary insomnia. Mirtazepine as mentioned above, has sleep promoting properties. It has been shown to increase SWS in normal volunteers [140] and to promote sleep in depressed patients[39] and may also have a place in the treatment of primary insomnia when fully investigated.

Chapter 4

Psychological Therapy in insomnia and depression

This chapter explores the treatment of primary insomnia or secondary insomnia (e.g. insomnia secondary to depression) using a cognitive behaviour therapy group approach

Patients with primary insomnia did report improvements in dysfunctional attitudes and beliefs about insomnia and improvements in energy/vitality and mental health, as measured by the SF36 quality of life scale, after attending group cognitive behavioural therapy (CBT). Sleep parameters were not significantly improved when compared pre and post CBT.

My role in this group work was in recruitment of patients, coleader of the insomnia groups, data analysis and the writing up of the results.

4.1 Introduction

The psychological management of insomnia is topical. Due to the potential problems of chronic benzodiazepine usage as detailed in chapter one and the cost of their prescription, the National Institute of Clinical Excellence (NICE) are strongly advocating the psychological management of insomnia.[57] This chapter will report some initial findings on group psychological therapy for people with chronic insomnia carried out on outpatients referred to a neuropsychiatry service in Bristol. The group work was carried out as part of a clinical service. In the introduction, the background of group therapy in insomnia is explained, as is the group programme. The outcome measures used

such as the Dysfunctional Beliefs and Attitudes Scale (DBAS) and the Quality of Life Questionnaire (SF-36) are then discussed followed by the results of five insomnia groups.

What really matters to the person with chronic insomnia? Clinical improvements in sleep parameters have much more relevance to patients than statistically significant results. Clinical improvements as defined by Espie (2001) [114] are:

(i) An increase in TST by 30 minutes

(ii) A decrease in SOL to under 30 minutes and/or a reduction by 50% or more

(iii) A decrease in WASO of 30 minutes and/or a reduction by 50% or more

(iv) A sleep efficiency of 80% or more

Relief of daytime symptoms, better sleep quality and being able to "carry on with the rest of their lives" are also more important to the sufferer than extra minutes sleep at night and/or falling asleep marginally faster.

In order to address these factors, studies on people with insomnia based in the community rather than in research trials or sleep laboratories have become important. These studies may include people with insomnia who may or may not be taking hypnotic medication.

Arguably, Cognitive Behavioural Therapy (CBT), forms the mainstay of treatment for chronic insomnia. It includes, stimulus control, sleep hygiene, relaxation, biofeedback, paradoxical intention, and cognitive therapy (see chapter one). Their individual effectiveness is discussed in chapter one, however it is increasingly common to use a combination of these treatment procedures known as multi-component behaviour therapy, multi-component CBT or usually 'CBT' to offer effective clinical management of insomnia, as some patients may respond better to some treatments rather than others.

Due to limited resources and cost effectiveness, it is also important to consider the mode of delivery of CBT. The use of CBT in a group setting has been carried out in the studies in Table 4.1. [114 141-145] They have all shown improvements in sleep parameters and other scales. However, they are difficult to compare because of inclusion criteria that use different definitions of insomnia (see chapter 1,) whether the participants were advertised for or presented for treatment, the different age-groups of the patients studied, the fact that they use objective or subjective sleep measures and the types of outcome rating scales used.

There have been three recent community research studies in UK general practice. In the first study, people with insomnia received CBT in a group format compared to a control group [114] (Table 4.1.) After 6 weeks, CBT was associated with a mean 30-minute reduction in SOL, and WASO. At 12 month follow up, TST was also improved by 30 minutes and over 80% of patients initially using hypnotics remained drug free. In the second, Espie (2007)[146], patients with insomnia received CBT in a group format compared to a control

group and were assessed by actigraphy, sleep diary, PSQI and SF36 (Table 4.1). Sleep diaries showed reductions in 60 minutes per night in SOL and WASO and a 9% increase in sleep efficiency. SOL was the most improved post group but SOL and WASO improvements were only partly sustained at follow up compared to sleep efficiency. The third study, also in general practice, was in an individual format.[117] Patients at 3 and 6 month follow up treated with CBT reported significant reductions in SOL, and improvements in sleep efficiency. They also had improved quality of life (SF-36 scale) and less hypnotic use than the non-treatment group.

Table 4.1: Summary of Group CBT studies for chronic insomnia

	Participants advertised for or presented for treatment	Diagnosis and Protocol	Controls	Sleep Diary/ PSG/Actigraphy	Outcome Rating Scales used	Follow up measurements
Espie 2007	Advertised for participants	Chronic primary and secondary insomnia in General Practice CBT vs Control	Yes	Sleep Diary/Actigraphy	PSQ SF36 HRSD ESS	Post group and 6 mths
Jansson 2005	Advertised for participants	Chronic primary and secondary insomnia CBT vs Self Help	Yes	Sleep Diary	HRSD DBAS	1 year
Backhaus 2001	Presented for treatment	Chronic primary insomnia (also excluded major depression) No Controls	Yes	Sleep Diary	PSQI BDI STAI	Post gp, 3, 12, 36 mths
Espie 2001	Presented for treatment	Chronic primary insomnia in General Practice (also excluded major depression) CBT vs CBT deferred vs Control	Yes	Sleep Diary/Actigraphy	PSQI BDI STAI PSWQ	Post gp, 12 mths
Morin1999	Presented for treatment and advertisements	Chronic primary insomnia (also excluded major depression) CBT vs Medication vs Combination vs Control	Yes	Sleep Diary/PSG	SII	3, 12, 24 mths
Jacobs 1996	Presented for treatment	Chronic primary and secondary insomnia	No	Self designed questionnaire	Nil	1 and 6 mths
Kupych-Wloshyn 1993	Presented for treatment	Chronic primary and secondary insomnia No Controls	No	Sleep Diary	Nil	Nil

Key to Table 4.1

Sl Hyg = Sleep Hygiene
STAI = State Trait Anxiety Inventory
PSG = Polysomnogram
DBAS = Dysfunctional Beliefs and Attitude Scale
ISQ = insomnia symptom questionnaire
PSQI = Pittsburgh sleep quality index
SII = Sleep Impairment Index
HSRD = Hamilton Depression Scale
PSQW = Penn State Worry Questionnair
ESS = Epworth Sleepiness Scale
BDI = Beck Depression Inventory

Recent evaluations of CBT for insomnia have been carried out through self-help approaches such as books, audio/video tapes, telephone support and the internet. Mimeault (1999)[112] tested self-help CBT 'bibliotherapy' (six booklets each covering a specific component of CBT) with and without supportive phone consultations against a waiting list control group. Compared to a control group, both treatment groups showed sleep improvements that were maintained at 3 month follow up. However, adding professional guidance to bibliotherapy produced further improvements. The presence of a therapist seems, therefore, to optimize treatment response. Bastien[111] (2004) also reported comparable effectiveness of CBT for primary insomnia delivered in an individual, group and telephone consultation format. This study was the first to compare different modes of delivery of therapist led CBT for insomnia. The results showed that CBT did not lose its effectiveness when delivered in a less costly format such as in groups or over the telephone. A study using an internet-based intervention produced a greater improvement in several sleep parameters relative to controls but the attrition rate was higher than in studies using face-to-face consultation visits.[113] There has also been a recent study comparing group versus individual CBT in primary insomnia[147] in which similar improvements were seen in sleep variables and quality of life scales between individual and group treatment, with these improvements being maintained at follow up.

4.2 Outcome Measures (Quantitative and Qualitative assessments of subjective sleep)

Quantitative and qualitative assessments of subjective sleep that are commonly used (see Table 4.1) are:

1) Sleep diaries. (see appendix 1 for copy)

2) Quality of life assessment (SF36). (Medical Outcomes Trust 1992[148]) (see appendix 4 for copy)

3) Visual analogue scales for Dysfunctional Beliefs and Attitudes about sleep questionnaires DBAS (Morin 1993[88]). (see appendix 4 for copy.)

1. Sleep Diaries

A seven-day measure of total sleep time, sleep onset latency and sleep quality as estimated by each group member for the previous night's sleep.

2. SF36 (Short Form 36) Quality of Life Scale

Quality of Life is a "complex and multidimensional term that has been defined as a concept encompassing a broad range of physical and psychological characteristics and limitations which describe an individual's ability to function and to derive satisfaction from doing so."[149] It includes the following domains, the physical, encompassing the ability to conduct activities of daily living, the psychological, or emotional, and the social, encompassing interactions with family, friends and community. Insomnia may affect each or all of these domains.

The SF36 quality of life questionnaire measures generic health concepts relevant across age, disease and treatment groups, and provides a comprehensive, psychometrically sound and efficient way to measure health from a patient's point of view by scoring standardised responses to standardised questions.

The SF36 was developed from the Rand Corporation's health insurance experiment in the USA, "The Medical Outcomes Study "(MOS).[150] This was a comprehensive evaluation of alternative methods of financing healthcare in the USA. The SF36 consists of eight multi-item scales containing two to ten items each and a single item measure of reported "health transition" (Table 4.2) SF 36 items are scored so that a higher score indicates a better health state. For example, functioning scales are scored so that a high score indicates better functioning and even the pain scale is scored so that a high score indicates freedom from pain. After data entry the raw data scores were recoded and transformed to a 0-100 scale using a computer software package. Scores between these values represent the percentage of the total possible score achieved. Transformed scale scores can be compared with norms derived from the Medical Outcomes Study and other published results based on the scoring rules.[151]

Concepts	Number of Items	Summary of content
Physical Function (PF)	10	Extent to which health limits physical activities e.g. walking
Role Physical (RP)	4	Extent to which physical health interferes with work or other daily activities
Bodily Pain (BP)	2	Intensity of pain and effect of pain on normal work in or outside the home
Role Mental (RE)	5	Extent to which emotional problems interfere with work or other daily activities
Social Function (SF)	4	Extent to which physical health or emotional problems interfere with normal social activities
Mental Health (MH)	2	General mental health including depression anxiety
Energy and Vitality (VT)	3	Feeling energetic and full of life versus feeling tired and worn out
Health Perception (GH)	5	Personal evaluation of health
Change in Health (HT)	1	Evaluation of current health compared to one year ago

Table 4.2: Health Concepts, numbers of items and summary of content for eight SF-36 scales and the health transition item.

Use of the SF36 in insomnia

As well as complaining about poor sleep, sufferers complain of impaired daytime functioning e.g. poor concentration, poor memory, tiredness and irritability. Indeed the ICSD definition and the DSM1V definition both include daytime consequences (see chapter one.) It has therefore been suggested that quality of life measures may reflect more accurately the daily impact of insomnia.

There have been only a handful of studies designed to evaluate the impact of insomnia on the quality of life. Hatoum (1998)[152 153]and Zammit (1999) [17] used the SF36 to evaluate the quality of life of a group of people with insomnia compared with good sleepers (Hatoum also controlled for demographic variables and co-morbid conditions), and showed insomnia is associated with significant quality of life impairments in all domains. As part of a European survey of severe insomnia [48], (chapter one,) SF36 scores were obtained on people with severe insomnia, and mild to moderate insomnia. The scores were then compared with controls in five northern European countries. SF36 scores were lowest in those with severe insomnia. The greatest range in scores was in:

1) Problems with work or activities resulting from physical ill health (role physical)

2) Social activities with family, friends etc (social functioning)

3) Problems with work and activities as a result of emotional problems (role mental)

Physical vitality was also particularly low among those with severe insomnia. In the UK sample SF36 scores for the severe insomnia group were compared to those obtained from a chronically ill population [154] and revealed on most domains the chronic severe insomnia group had worse quality of life scores than those patients with chronic physical illness.

Leger (2001)[155], after controlling for anxiety and depression, also compared SF36 scores in 3 groups of people with insomnia, DSM 1V defined

insomniacs, a matched group of people with mild insomnia, and a matched group of good sleepers. They found a gradation between the three groups, confirming that the more severe the insomnia the worse the quality of life. They found that eight out of nine dimensions of the SF36 were significantly worse in people with insomnia than in good sleepers. All groups estimated that their health status at the time of the study was on average similar to that of the previous year. Leger suggests this is because insomnia impairs quality of life progressively over several years and to a lesser extent in the short term.

More recently, Morgan (2003)[117] took a wide range of people aged 31-92 years from general practice with insomnia. He carried out a randomized controlled trial comparing people who had had a CBT (individually), and those who had had no additional treatment by post treatment assessments starting at 3,6, and 12 months. As well as measuring sleep quality (see chapter 1) the SF36 was measured at these intervals. They found statistically significant improvements in energy and vitality at 3 months, physical functioning at 6 months, and mental health at 6 months in the people that had received CBT.

3. Dysfunctional Beliefs and Attitudes Scale (DBAS) Morin 1993[88]

The scale comprises 30 items (see appendix for copy.) There are five subscales:

1. Misconceptions of the causes of insomnia
2. Misattributions or amplifications of the consequences of insomnia
3. Unrealistic sleep expectations
4. Diminished perceptions of control
5. Faulty beliefs about sleep promoting practices

Morin (2002)[156] used the DBAS scale to assess if changes in beliefs and attitudes about sleep are related to sleep improvements after treatment of insomnia. Older adults with chronic and primary insomnia received CBT, pharmacotherapy (PCT), combined CBT and PCT or a medication placebo. In addition to daily sleep diaries and sleep laboratory measures, the participants completed the DBAS at baseline and post- treatment. The results showed that CBT and combined treatment produced greater improvements of beliefs and attitudes about sleep at post-treatment than PCT and placebo. Reductions of DBAS scores were significantly correlated with improvements in sleep efficiency as measured by daily sleep diaries and by polysomnography.

Since 1999, in response to clinical need and the availability of suitably trained staff at two centres in Bristol, we have been able to combine to set up one of the few clinical group treatment programmes in the UK for the treatment of chronic insomnia. This was aimed at helping people cope with chronic insomnia whatever the initial cause and was based on the report of group therapy for insomnia carried out in Toronto, Canada in the mid 1990's by Kupych-Wloshyn and Colin Shapiro.[157]

A number of factors motivated us to establish the insomnia groups. Firstly, the group approach was considered a cost effective way to treat several patients simultaneously. Secondly, we had a number of difficult to treat people with insomnia at our clinic for whom other therapeutic interventions such as medication had not been totally effective. Thirdly, we sought to provide an

alternative strategy for helping these patients to give them optimism about a different treatment approach (realising that many of the patients had previously received various components of the treatment package individually.) We were hoping to expose the participants to therapeutic factors associated with group work. The kind of therapeutic factors associated with group work are listed below (Yalom 1985):[158]

(i) Instillation of hope

(ii) Universality

(iii) Imparting of information

(iv) Altruism

(v) Development of socializing techniques

(vi) Imitative behaviour

(vii) Catharsis

(viii) Corrective recapitulation of the primary family group

(ix) Existential factors

(x) Group cohesiveness

(xi) Interpersonal learning

The outcome measures described above were chosen to assess the outcome of the insomnia groups. The sleep diary gave a subjective interpretation of how a participant thought they slept at the beginning of the group programme compared to at the end.

The SF36 was chosen to measure any changes in quality of life from the start of the first group to the end of the group sessions. (Daytime functioning, quality of life and insomnia are known to be closely related in people with insomnia as discussed above. [155]) The DBAS scale was chosen to see if seven weeks of group work could change attitudes to insomnia which would therefore improve the subjective sleep of participants.[156]

(The initial four groups run were pilot groups with differing session content in each group and not all the outcome measures were obtained. The data from these groups was not therefore analysed.)

4.3 Components of treatment group

The groups were led by a doctor (sleep specialist), two occupational therapists and a research sleep scientist. There could be a different combination of leaders at each session but there are always two group leaders present.

The occupational therapist assessed potential participants. Qualities sought before entry to the group were willingness to try a group as a form of treatment, and commitment to the programme of sessions. Patients with depression were included as long as they were well enough to attend and participate.

Participants joined the group whether they were taking sleep related medication or not. If any group members were keen to use the support of the group to decrease hypnotic medication or to cease taking hypnotics they were encouraged to do so. "Homework" and completion of sleep diaries were also part of the programme as was small group work (splitting the group members into two groups of no more than three members, so each group member could

discuss their sleep problems individually with the group leader.) Individuals were encouraged in the small groups to work, each week, on their own specific insomnia solutions. Informal support from other members of the group was also encouraged. Group courses lasted seven weeks and each group had a maximum of eight participants.

4.4 Group Programme

The programme consisted of seven ninety minute sessions spread over seven weeks. The format and timetable of the group sessions is shown below:

<u>Week 1</u>

Introduction and explanation of group rules. We asked what do the group members understand by "insomnia?" Individual goals for each group member were written down on a flip chart. Information was given about sleep science and sleep architecture to educate and inform group members. Detailed information was provided about sleep hygiene, stimulus control, thought stopping, imagery and paradoxical intention techniques. Small group work was used to discuss putting into practice the techniques suggested above and explanation was given about the use of individual sleep diaries. The concept of using a sleep diary for the next 7 nights was explained. Group members completed the SF36 and DBAS.

Week 2

Cognitive Therapy (1)

There was an introduction to the principles of cognitive therapy and challenging "Negative automatic thoughts" (NAT's) about sleep and insomnia. We used the DBAS completed in the previous week to identify personal underlying beliefs about insomnia. We set homework to try and practice challenging personal NAT's and to write these down. There was further small group work.

Week 3

Cognitive therapy (2)

There was revision of challenges to personal NATS about insomnia using their homework examples and/or examples from the attitudes and beliefs about sleep questionnaire (DBAS) . There was further small group work to review group members sleep using the suggested techniques.

Week 4

Relaxation (1)

The senior occupational therapist performs an hour's relaxation session based on a method derived from progressive muscular relaxation.[159] The group members are trained to be aware of muscle tension by first tensing and then relaxing certain groups of muscles. Some autogenic relaxation techniques and imagery techniques are also used. Autogenic relaxation differs from progressive relaxation in that while both seek to induce a state of muscular relaxation, autogenic relaxation aims to involve vasomotor and cognitive

processes as well.[160] This is achieved by teaching the trainee a series of mental exercises involving sensations of heaviness and warmth. Tapes for home use were also given out

Week 5

This was a session centered on questions and discussion about past or present medication. There was further small group work.

Week 6

Relaxation (2)

Time for general discussion of topics to do with sleep bought up by members of the group. Further questions about sleep science answered.

Small groups and sleep diary given out to return for week 7.

Week 7

Completion of post group SF36 and DBAS

Feedback comments were asked for from the group members about the course in an open feedback session in the last group. Participants were then asked to fill in a written feedback sheet with comments that could remain anonymous if they so wished.

Sleep diary results comparing week 1 and week 2 were reviewed.

A follow-up meeting in 3 months time was organised.

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4.5 Statistical Analysis

Week one and week seven means of the self rated sleep diary, for SOL, TST, and sleep quality were compared by a paired t test. Similar comparisons of week one and week seven scores were made for the SF36 and DBAS.

4.6 Results

Number people referred.	43
Attended assessment interview	41
Commenced group	38
Completed at least 5 of 7 sessions	34

Table 4.3: Referrals for five insomnia groups

The demographic table shows people with chronic insomnia attending the group were predominantly female > 70%, and aged between 45-60 i.e middle aged. Most participants had had insomnia for under 10 years but over 2 years (50%) but the second largest group had had insomnia for between 10 and 20 years (30%). 30% had a psychiatric diagnosis of depression and or anxiety. Over 50% of people were taking hypnotics while approximately 30% were taking antidepressants.

Data from the five groups was analysed. However, only 23 pairs of sleep diaries were completed for a variety of reasons mostly because of non-attendance at week 6 or non-return of sleep diaries at week seven. Some diaries were completed incorrectly. Non-completion of sleep diaries in the first week also occurred, as occasionally some people joined the group after the first session and therefore did not complete a pre treatment sleep diary. People had

absences from the group because of holidays, illness and work/children commitments that also affected data collection. The SF36 and DBAS scales had more data available for analysis n=33, because patients completed the questionnaires during group time and it was therefore possible to collect more complete data.

	n=38	%
Male	14	27
Female	24	73
Age Range (22-77)		
<30	7	9.5
30-45	7	9.5
45-60	23	60
>60	1	3
Duration of insomnia		
<2 years	4	11
<10 years	19	50
10-20 years	12	31
>20 years	3	8
Status		
Married/Partner	22	58
Single	13	34
Divorced	3	8
Occupation		
Employed	13	34
Unemployed	7	18
Student	2	6
Retired	4	11
Housewife	12	31
Psychiatric Diagnosis		
Depression /Anxiety	12	31
Medication		
Hypnotics	20	53
Antidepressants	14	27
Concomittant illnesses	5 Hypertension n=2, Irritable Bowel Disease, Retinitis Pigmentosa, Endometriosis	13

Table 4.4: Demographic characteristics of group participants (n = 38)

Sleep Diaries

n=23

	Mean week1 Start of group	Mean week7 End of group	sd	t statistic	p value
SOL(mins)	75.0	64.2	35.1	1.02	ns
TST(hours)	5.3	5.4	1.0	-0.6	ns
sleep quality	4.3	4.6	1.3	-1.2	ns

Table 4.5: Results of paired t tests comparing mean scores at weeks 1 and 7.

There were no significant differences between SOL, TST and sleep quality results after the seven-week insomnia group programme (Table 4.3). Initial three-month follow up results are shown in the following table. Statistical analysis was not carried out on this data due to small numbers.

Sleep onset latency	Number (%)	Total sleep time	Number (%)
Worse.	5(31.2)	Worse.	5(31.2)
Improved	11(68.8).	Improved	11(68.8).
>30 minutes less	3(18.8).	>30 minutes more	9(56,3)

Table 4.6: Numbers of participants showing change in sleep (compared with start of course) at three-month follow-up (n = 16) [161]

SF36 results (n=33)

There were statistically significant results after the insomnia group programme in the following domains of the SF36 quality of life measure (Table 4.5):

- Mental Health
- Energy and Vitality
- Health perception
- Social Function and Role Physical very nearly reached significance

	Mean week 1 Start of group	Mean week 7 End of group	sd	t statistic	p value
Physical Function (PF)	81.4	82.4	15.3	-0.7	0.693
Role Physical (RP)	36.4	47.7	33.3	-2.0	0.06
Role Mental (RE)	43.4	53.5	49.0	-1.19	0.243
Social Function (SF)	51.2	59.3	23.4	-1.99	0.055
Mental Health (MH)	52.8	59.4	15.6	-2.4	0.022
Energy and Vitality (VT	27.5	34.4	13.4	-2.94	0.006
Pain	66.0	71.2	21.2	-1.4	0.172
Health Perception	49.2	56.6	11.9	-3.62	0.001
Change in Health (HT)	43.9	48.5	21.2	-1.23	0.230

Table 4.7: Comparison of SF36 scores at weeks 1 and 7 (n = 33)

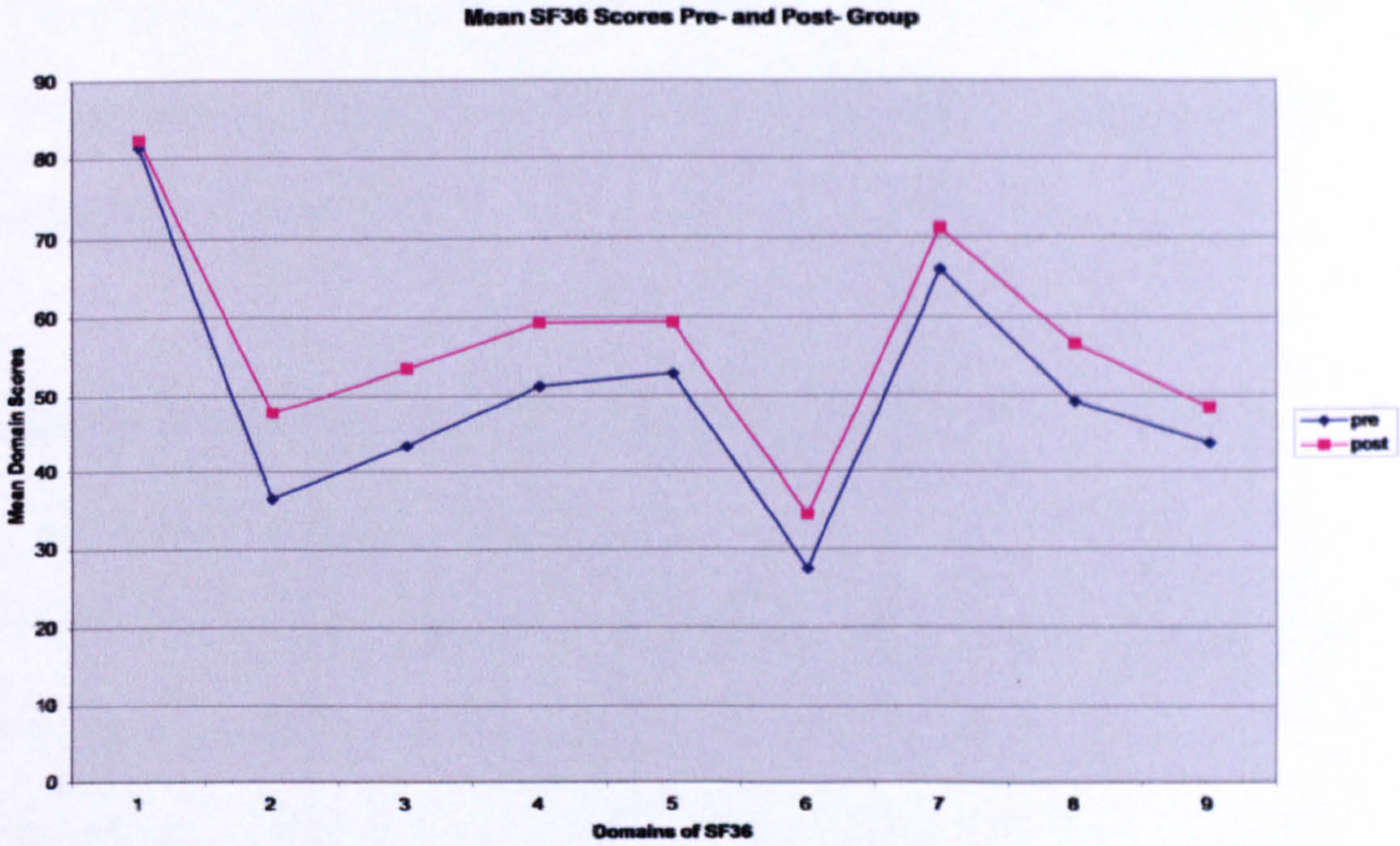

Figure 4.1: Graph of mean SF36 scores pre (week1) and post (week 7) group therapy

Domain

1 = Physical Function

2 = Role Physical

3 = Role Mental

4 = Social Function

5 = Mental Health

6 = Energy & Vitality

7 = Pain

8 = Health Perception

9 = Health Transition

DBAS (n = 33)

There was a statistically significant difference between the mean DBAS scores of the 30 item questionnaire between week 1 and week 7, t statistic= 4.1290 and p value = 0.0002

Feedback from open discussion and written sheets

The general feedback points were:

Information about the most up to date techniques to help coping with chronic insomnia was thought to be useful.

The support of the group members was also well appreciated.

The specific sessions on cognitive therapy were applied well by most people and were thought to be something that they could not learn easily or practice elsewhere.

The medication session was also liked in the way it helped to disentangle misinformation or confusion about the medical treatment of insomnia.

The small groups were also popular due to the time that was made available for individual assessment of group members' sleep.

Negative comments were few.

Members in one group exchanged names and addresses and met up to continue supporting each other. A summary of the common themes in feedback is shown in Tables 4.8 and 4.9.

	Percentage
Support and sharing ideas with others with similar problems.	51
'Finding that I am not alone'	33
Ideas and strategies	33
"Expert advice" the facts	30
Informal, open and frank discussion.	16
'Finding that I am not as bad as others.'	4

Table 4.8: What participants liked about the course and percentage mentioning each factor (respondents could mention more than one item)

	Percentage
No change.	44
Improved sleep (unspecified)	31
Improved sleep quality.	19
Increased total sleep time.	13
Uncertain	6
More relaxed about insomnia; more positive	31

Table 4.9: Reported changes in sleep at the end of the course and percentage mentioning each factor (respondents could mention more than one item)

4.4 Discussion

It is acknowledged that the data presented in the results are from a clinical pragmatic group. Participants could enter the group as long as they complained of persistent insomnia whatever the cause. (They had primary insomnia or secondary insomnia e.g. due to depressive illness or other medical conditions.) They could also be "on" or "off" medication or taking it on an as needed basis. We wanted to know if our group made a difference subjectively to people suffering from long-term insomnia at a clinical level and if we could help them move on in their lives instead of getting "stuck" with their insomnia.

In summary, the sleep diary results from these five groups show no statistically significant changes for the sleep variables TST, SOL or sleep quality after seven weeks. However, there were statistically significant improvements in quality of life scales in mental health, energy and vitality and health perception. Social function and "Role Physical" (i.e. how a person can function physically at home and in the work place,) also came close to statistical significance after the seven-week course. There were also highly significant decreases in dysfunctional attitudes and beliefs about insomnia as measured by the DBAS.

Sleep diaries

Comparison of these results with other data is difficult. Most of the studies carried out previously have been on individually treated patients in a research

setting. Patients in these studies had a diagnosis of primary insomnia and they were often comparing two treatment modalities i.e. CBT versus medication or CBT versus control. Outcome measures used in these studies have been objective (e.g. polysomnogram) and/or subjective (e.g. sleep diary) and have concentrated on statistical rather than clinical significance. Furthermore, there has been little research performed on quality of life, usually considered a secondary sleep variable, and this may be more important to the patient than improvements to their sleep. Table 4.7, in the introduction to this chapter, shows the trials to date that have compared CBT, performed in a group setting, versus either a waiting list control and/ or medication.

One of the relevant studies with which to compare these data, due to patients being treated in a group setting, was with a group of patients with insomnia from general practice in 2001. Trained health visitors taught CBT over a six-week course. In this research trial 139 insomniacs were randomised to either CBT or a self- monitoring control (SMC) group. CBT consisted of six group sessions with 4-6 patients in each group.[114] After the controlled phase SMC patients entered deferred treatment. Follow up was post-treatment group, post-SMC deferred treatment, and at 12 month post-treatment group. After 6 weeks CBT was associated with a mean 30 minute reduction in SOL, and WASO. However, TST was increased by a mean of 30 minutes in both the treatment group and the deferred group only at 12 month follow up. The CBT deferred group showed the same changes in SOL and WASO after they had received the 6 weeks of treatment. In an analysis of outcome data at 12 month follow up, the sleep improvements were maintained.[162] Two thirds of patients achieved

and maintained a sleep latency of 30 minutes or under and a similar proportion achieved 30 minutes or less wakefulness during the night. Almost half of the patients reduced sleep latency and night-time wakefulness by 50% or more.

These results are broadly comparable with the 1999 American Sleep Societies Meeting (ASSM) meta-analysis article [107] (see chapter 1). The meta-analysis states that between 70-80% of insomnia patients benefit from CBT treatment, with 50% achieving "clinical meaningful outcomes" and about a third becoming good sleepers.

Similarities between Espie's study and the Bristol clinical insomnia group were that in both studies patients carried on taking sleep related medication as prescribed unless they wanted to decrease or stop it. However, Espie had much larger numbers, there was a control group and they recruited from general practice rather than hospital outpatients. The Bristol group above may have been a more difficult patient group to treat as Espie excluded patients with major depression, while this insomnia group had patients with mild to moderate depression (albeit they were deemed to be well enough to take an active part in the group). The patients in these insomnia groups could have had more severe insomnia as they were recruited from a hospital rather than general practice setting, but comparison of the chronicity of insomnia between the people in these groups and Espie's, shows most people had had insomnia for between 2 and 10 years and 10 and 20 years, however in Espie's groups there were also a similar proportion of people with insomnia for over 20 years. Length of insomnia problems do not necessarily predict severity. With respect

to treatment outcome, Espie performed a regression analysis based on his 2001 study using a number of pre-treatment variables, and showed that initial severity of insomnia and the use of medication for insomnia did not predict a poor outcome with CBT.[162] Espie (2001b)[162] also followed up patients at 12 months compared to the three month follow-up described in our study.

The sleep diary results in our study showed no statistically significant results in any of the sleep parameters. However, the numbers are small and a trend exists towards a clinically meaningful result to the patient e.g. clinical significance. It is possible that we followed up our patients too soon. However, the three-month post-group follow-up was determined by clinical as well as research needs. Espie only had statistically significant results for TST at 3 month follow up and not immediately post group therapy.[114] This could indicate that follow up at 3, 6 and 12 months is more important than directly post-group, and that outcome should not be assessed directly after group work for insomnia.

The other group CBT studies[114 141-145] all found subjective and objective improvements in sleep after CBT in a group format up to 3 years after treatment. This is consistent with meta-analysis findings that demonstrate that individual CBT for chronic insomnia has a lasting effect. Medication for chronic insomnia, by comparison, is only effective as long as it is taken.[116]

Recruitment factors are also important. Jansson (2005) and Morin (1999) used advertisements to recruit patients while all the other studies in the Table 4.6 used patients presenting for treatment. Therefore in these two studies there are

patients who sought treatment who may differ from individuals who do not seek treatment. It may be that patients seeking treatment have higher psychological distress and may respond to treatment differently. Also, Espie (2001) was not the only study cited in table 3.4 to exclude patients with mild to moderate depression i.e. secondary insomnia. Patients with depression, as well as those with drug dependant insomnia may be those most likely to present to sleep clinics and doctors, be more refractory to treat but also in the most in need of treatment.

Espie (2001b)[162] examined age and other demographic factors and found they were not of significant predictive value for a good outcome to CBT treatment. Indeed symptoms of anxiety and depression (note these patients were not depressed), and thinking errors positively predicted good outcome. Neither gender nor occupational status differentiated responders from non-responders. This has also been demonstrated in Espie's most recent study of group CBT for insomnia in 2007.[146]

Patient perceived improvement is also extremely important as discussed in chapter one. Negative cognitive appraisals appear to be instrumental in perpetuating the cycle of emotional arousal and insomnia and therefore may be the most relevant factor in the aetiology and maintenance of insomnia and its consequences, including increased health care utilization. If patients do not perceive improvement in insomnia symptoms the insomnia has not been effectively treated since the failure to alter sleep perceptions will likely perpetuate the insomnia cycle. Therefore the results of patient's cognitive

attitudes and beliefs after treatment in the insomnia group, as discussed below, are crucial.

SF36 (Quality of Life.)

The treatment of insomnia with CBT in this study improved Mental Health, Energy / Vitality and Health Perception post group and had a nearly statistically significant effect on social function and role physical.

One of the few studies to have compared SF36 scores before and after CBT was by Morgan (2003.)[117] This was not in a group format and outcome measures were not conducted directly after the end of the treatment group but at 3-6 months follow-up. However, Morgan found that the domain of Energy and Vitality improved at 3-month follow up which is compatible with these results. At 6-month follow-up, he found that physical function and mental health scores were also statistically significantly improved and this result also appears to concur with these findings. Espie (2007) is the first study to use the SF36 pre and post group CBT (which is directly comparable to this group programme.)[146] They had time effects on ANOVA on the four domains: physical functioning, mental health, energy/vitality and health perception. Significant group time interactions, suggesting treatment response after CBT were obtained for two domains: mental health and energy/vitality. This is in agreement with my results where mental health and energy/vitality were significantly improved. It would be interesting to see whether the improvements in SF36 scores in this group were maintained at 3, 6, and 12 month follow up and this is an avenue for further work.

DBAS Cognitive Attitudes and Beliefs

The data shows a very significant improvement in beliefs and attitudes in sleep after CBT. This is in agreement with all the other research into changes in the DBAS with CBT. Edinger (2001),[163] showed that individual CBT provided larger changes on the DBAS in insomniacs than relaxation or a sham behavioural intervention. These changes persisted during the follow up period. Morin (2001),[156] also demonstrated that changes in beliefs and attitudes about sleep are related to sleep improvements in the treatment of insomnia. In his 1999 study, comparing the efficacy of group CBT and pharmacotherapy for late life insomnia, patients completed the DBAS at baseline, post-treatment and at 3, 12, and 24 month follow up assessments after they had been assigned to individual CBT, pharmacotherapy, a combination or a placebo group. The results showed that CBT and combination treatments produced greater changes of beliefs and attitudes about sleep at post-treatment than pharmacotherapy and placebo. Reductions of DBAS scores were significantly correlated with improvements in sleep efficiency as measured by daily sleep diaries and by polysomnography. Post-treatment DBAS scores were also significantly correlated with sleep efficiency at each of the three follow up assessments at 3, 12 and 24 months. This is a similar outcome to that found in Jansson's study.[141] At the one-year follow-up in Jansson's study, 64 of CBT treated patients had a 23% reduction in DBAS scores compared to an 8% reduction in the control group.

Findings relating to changes measured by DBAS raise the question whether changes in attitudes and beliefs are essential to treat insomnia effectively? This idea would be supported by Morin's results as he found significant correlations between the magnitude of changes on sleep-related beliefs and attitudes and the degree of sleep improvements at post-treatment.[156] Furthermore, Morin found that the strength of the relationship between cognitive changes and sleep improvements increased over time. Morin also points out that patients treated with CBT obtained DBAS scores that were comparable to those obtained in older adults without insomnia complaints in two other studies. [137 144] Changes in thoughts about sleep were more strongly associated with subjective (sleep diaries) than with objective (PSG) sleep improvement. This finding could be explained by the fact that untreated insomniacs may overestimate their sleep problem and underestimate their sleep duration i.e. they have sleep misperception. As cognitive therapy addresses such misperceptions, patients treated with CBT may perceive their sleep more accurately over time which in turn contributes to a stronger relationship between cognitive changes and subjectively assessed sleep improvement.

Scores on the DBAS have also reduced when CBT is delivered in other modalities. As mentioned above, Bastien and Morin (2004) showed the DBAS was significantly reduced post treatment in all treatment modalities i.e. individual, group and telephone consultations. Strom (2004)[113] investigated the effects of internet based CBT treatment for insomnia. Compared to a control group there was also a significant decrease in DBAS scores.

The DBAS reveals that stronger beliefs in the negative long-term consequences of insomnia motivation are associated with a good SOL outcome (e.g. " I am concerned that chronic insomnia may have serious consequences on my physical health") providing supporting evidence that dysfunctional thinking may be a positive indication for the CBT treatment of insomnia and that there is a "cognitive pathway" for mediating treatment effects. It is, however, important to emphasise that most CBT for insomnia analyses only considered pre-treatment variables that influence outcome. Many other factors can play a part in the prediction of clinical response, including readiness to change, motivation and compliance.

In summary, in this study of a pragmatic clinical group therapy for chronic insomnia statistically significant changes in attitudes and beliefs about insomnia and improvement in quality of life were found. There were no significant changes in subjective sleep outcome variables such as TST and SOL. Patient satisfaction with the group was high. Further work should include collection of more outcome data post-treatment at intervals up to a year or longer after the end of treatment, particularly concentrating on quality of life data such as the SF36. This will help establish if the effects of CBT are long lasting. It would also be useful to encourage reduction or discontinuation of medication in the group participants.

Chapter 5 Conclusion

This series of studies has examined the treatment of insomnia both in depression and chronic insomnia. There are two pathways to effective treatment, medication and psychological treatment.

In chapter two nefazodone, as a treatment for insomnia in depression, is discussed. After the demonstration that nefazodone improved sleep continuity in depressed patients with insomnia it was decided to investigate the use of nefazodone as a drug treatment in chronic insomnia (chapter 3).

Psychological treatment in insomnia is reviewed in chapter one and at the beginning of chapter four. In chapter four the outcome data from five insomnia treatment groups is analysed and discussed.

The treatment of depression with medication must be paramount if someone has moderate to severe symptoms and has suicidal thoughts. Chapter two demonstrates that nefazodone is more effective at relieving the sleep symptoms of depression than paroxetine particularly at the beginning of treatment when patients complain most bitterly of sleep problems. Significant differences showing that nefazodone improved Total Sleep Time, Sleep Efficiency and decreased Number of Awakenings compared to paroxetine. This was demonstrated after 3 days of treatment and clinically this is important as over 90% of patents with depression suffer from insomnia. Unfortunately, nefazodone is now not prescribed due to the rare but serious side effect of

hepatotoxicity. However, its sister compound trazodone is available, used quite widely and is thought to treat sleep complaints in depression (although grade I evidence from a placebo controlled trial for this is lacking.) The antidepressant mirtazapine is also effective at relieving sleep symptoms and is also used clinically when sleep complaints are a major problem for the patient with depression.

A natural follow on to the nefazodone in depression study described in Chapter 2 was an investigation into nefazodone's effect on sleep in patients with chronic primary insomnia. The results in chapter three show that, in the small group of patients studied, nefazodone did not have a significant effect on sleep in patients with chronic insomnia contrary to the patients with depression. (The primary outcome variables studied were Sleep Onset Latency, Total Sleep Time and Number of Awakenings.) A follow up study is being carried out at the present time in our department to establish the effect of trazodone on sleep in patients with primary insomnia.

One of the reasons for the disappointing results in the nefazodone in insomnia study may be that some of the subjects recruited were suffering from "sleep misperception"(SMP) and depressed patients with insomnia show less sleep misperception.[99] Subjects in this trial, who were recruited, complained bitterly of poor sleep subjectively but this was not verified via polysomnography. The sleep efficiency of most patients in chapter 3 while on the placebo arm of the crossover trial was no lower than 80%. Some patients in the study may, therefore, have had less severe insomnia when measured objectively than we

had anticipated. Consequently, the results were very variable and no overall improving effect was detectable. Insights into SMP may be useful to extend the approach when trialling a drug to help treat chronic insomnia, and develop psychological treatments, as is investigated in chapter 3 and in chapter four (discussed later.) On recruitment to a medication trial for chronic insomnia, a baseline PSG may have been useful to establish the degree of SMP in each potential subject. The worst SMP subjects could then be excluded before randomisation.

In Chapter 4 the psychological treatment of insomnia is discussed. I report on five groups of patients who had been referred to a tertiary centre for the treatment of insomnia. Overall, the participants liked the insomnia groups. They found them supportive and informative. Analysis of the sleep diary data showed no statistically significant improvement in Sleep Onset Latency, Total sleep Time and sleep quality, but there was a trend towards improvement in these variables. However, there was a large statistical difference in the Dysfunctional Attitudes and Beliefs Scale pre and post group with decreased scores post group. There was also a statistically significant difference in improved energy/vitality and mental health scores from the SF36. This shows that the group treatment improves dysfunctional beliefs and attitudes about sleep and therefore perhaps when larger numbers are analysed this could also result in a statistically significant improvement in sleep measures.[146]

Sleep misperception is a well-recognised phenomenon in people with chronic insomnia, see chapter one, and very relevant to the psychological management

of insomnia that is discussed in chapter 4. While running the insomnia groups there have also been a handful of patients who at the end of the group, by their oral and written feedback, and diary data, have made little or no progress in coping with their insomnia or moving on with their lives. The common statement is usually along the lines of: "All I know is that I used to sleep, I know what that is like, but I am not doing that now." This is despite polysomnographic evidence that showed over 6 hours sleep in two of these individuals. However, when looking at the individuals with the worst SMP in the groups reported on, the SF36 results they have still shown improvement in energy/vitality and mental health scores and therefore benefited in improved daytime functioning.

Suggestions for future treatment of SMP/subjective insomnia might involve trying to improve the accuracy of their sleep perceptions. This might consist of using perceptual retraining with immediate accurate feedback following awakening. Downey(1992[164] showed that a procedure designed to improve normal sleep/wake discriminations among those with sleep state misperception led to a reduction in sleep complaints, (although they had no control group of patients with objective insomnia). It was hypothesized that subjective insomniacs could more accurately estimate sleep latency by learning to differentiate wakefulness from sleep by EEG training while awake. Ten subjective insomniacs were randomly assigned to one of two groups. Group 1 subjects participated in both a control and a training week; group 2 subjects participated only during a training week. During training, subjects were taught to use sleep markers (A, B or C) to help them more accurately estimate sleep

latency and were given feedback about the accuracy of their estimates. Marker A corresponded to an electroencephalographic level of wakefulness; marker B corresponded to the initial sleep spindle; marker C corresponded to 5 minutes of continuous sleep after the first sleep spindle. In the control condition, subjects had no feedback and were not taught to use markers to help them judge sleep from wakefulness. After training, subjective sleep latency, correctness of estimates of sleep versus wakefulness and perceived ability to fall asleep significantly improved. They concluded that subjective insomniacs could learn to more accurately estimate sleep from wakefulness with the use of sleep-wake markers. More recently SMP, and the anxiety connected with it, has been shown by Tang (2004) to be reduced by careful comparison of sleep diary data and actigraphic data.[138] A group of insomniacs were asked to keep a sleep diary and wear an actigraph for three days. Half of the group were then shown the discrepancy between the diaries and actigraph and half were not. Sleep was then recorded for another 3 days and the group, who had had the discrepancy discussed with them showed an improvement in the recording of their SOL in the next few days of recording and less anxiety about their sleep. Tang and Harvey (2006)[139] have repeated their 2004 pilot study comparing a behavioural experiment to the verbal feedback i.e education about SMP. They also added other outcome measures other than sleep measures and used a sample population from the general public rather than university students. The participants in the behavioural experiment group calculated their own sleep misperception with guidance while those in the verbal group were told of their sleep misperception, (which was calculated for them.) The participants were then monitored for another 2 nights. Consistent with the hypothesis the

behavioural group had better results on their sleep misperception scores and other sleep measures and rating scales. This would support behavioural experiments giving larger therapeutic changes than verbal techniques and changing the way people think and feel about their sleep. However both verbal and behavioural techniques gave improvements in SMP and it is promising clinically that simple verbal feedback will help improve subjective measurements of sleep which are extremely important to the patient. Tang and Harvey recommend further research with this technique with a wider population sample and to discover if the effect on lowering SMP is sustained over a period of time. They also suggest that this technique could be included in a multicomponent cognitive behaviour treatment plan for insomnia to help improve success rates.

It is also thought that the subjective misperception of sleep immediately on waking may contribute to the maintenance of insomnia by impairing daytime functioning with more negative thoughts during the day. Semler and Harvey (2005)[96] has shown that perception of a "good nights sleep" versus a "poor night's sleep" immediately on awakening was associated with impaired daytime functioning even when objective measures showed very similar sleep patterns via actigraphy in both groups of sleepers. It therefore may be important to correct an insomniac's bias towards reporting wakefulness. This could consist of providing information and reassurance that mental activity persists during sleep and extended periods sleep overnight are often interspersed with periods of wakefulness.

It could also be helpful to use cognitive therapy to directly challenge negative beliefs immediately on waking that may then lead to less distress during the day and possibly a better night's sleep the following day. We have certainly tried this approach as add-on therapy in a patient who has documented SMP and had already been through the insomnia group programme.

Could these extra techniques be adopted into an insomnia group programme like the one described in chapter 4 to particularly help people with insomnia and SMP? Perhaps a second group programme could be arranged for those that had SMP with some extra cognitive work together with a PSG and behavioural intervention afterwards to learn what SMP is and how it can perpetuate insomnia.

The recent NICE guidelines make a number of references to the non-pharmacological treatment for insomnia. They suggest that, if available, non-pharmacological methods should be tried before any pharmacological treatment for short- term insomnia. However, NICE make no recommendations about how to help patients with long-term insomnia. There are, however, few resources in the UK at present for the non-pharmacological treatment of insomnia. This is why reports of clinical effectiveness of a group insomnia programme for chronic insomnia run within the NHS are so important. The next stage after establishment of such programmes is to encourage reduction of medication during them. In reality, a large percentage of patients with insomnia take hypnotics intermittently for longer than the 2-4 weeks recommended by the hypnotic manufacturers. The only other effective

treatment for these patients is non-pharmacological i.e. cognitive behaviour therapy (CBT) in an individual or group format.

With respect to CBT for insomnia, our results show improved quality of life scores and dysfunctional beliefs scores although little improvement in sleep parameters. This was in the context of a clinical pragmatic service for patients with primary and secondary insomnia. Harvey 2003[165] argues that an effect size of 0.9 for SOL, 0.6 for WASO and 0.5 for TST in meta-analyses by Morin (1994)[106] and Murtagh and Greenwood (1995) [108] of randomised controlled trials for CBT in insomnia were markedly lower than effect sizes obtained for other psychological disorders such as depression. The effect sizes in these papers were, in fact, z scores which can be interpreted as the distance, in standard deviation units, between the average treated and the average control patient. She argues that 'We should not rest yet' and that we should improve the methodology and reporting of RCTs so that the results reported are not under- or overestimates and we should seek to improve CBT for insomnia. There are still 25% of people not showing any response to CBT.[107] We would agree that there is room for improvement particularly when dealing with patients who have "racing thoughts" which are not obviously "affect laden" but come into patients' minds when they are lying awake and can't get to sleep. Paradoxical intention, imagery and thought stopping can all be used but do not provide a perfect solution to these annoying thoughts.

A group method is certainly potentially time effective and can be cost effective, although evidence comparing the efficacy of group or individual

CBT is lacking. A very recent study by Espie (2007) has shown nurse-administered small group CBT for chronic insomnia was effective.[146] This study however is also important, as CBT in this study is associated with significant positive changes in mental health and energy/vitality, (using the SF36) which agrees with our clinical group format findings. It was also showed in this study, via regression analysis, that the chronicity of the insomnia, the absence or presence of physical and mental health co-morbidities and participant age and sex was not associated with response to CBT.

Treatment delivery (chapter1), dosage (chapter 1), acceptability (chapter 4), adherence, accessibility, and cost effectiveness of CBT for insomnia are all important to consider. A recent publication by Edinger 2007, looked at dose – response for individual CBT finding twice weekly for eight weeks was the most effective. Stinson and Harvey (2006) also recently assessed the barriers to seeking treatment for primary insomnia in the UK.[166] Reasons for not seeking treatment were that people thought their insomnia was benign or trivial and they should be able to "cope on their own." There was also a lack of awareness of treatment options and a perception that what was available was ineffective. There is little research as to whether patients find CBT acceptable but the indications from running the insomnia groups reported in chapter 4 show these insomnia groups were well liked by participants.

Accessibility is a problem because of the lack of clinical CBT programmes running in the UK. Adherence during and after CBT treatment has been measured in a few studies and Harvey 2002 has shown that stimulus control,

sleep restriction and cognitive restructuring are used in preference to other techniques and reported adherence to stimulus control and sleep restriction was the strongest predictor of clinical sleep improvements.[167] In the insomnia groups described above stimulus control and cognitive restructuring were being used at three-month follow up when group participants were questioned.

Is a combination of medication and CBT the best alternative for those people with chronic insomnia? Morin would support this to maintain the best short and long term outcomes however acknowledges that acute insomnia is more easily treated with medication that is readily available with rapid relief of symptoms.[168] In the case of chronic insomnia perpetuating factors should be addressed and CBT used for more sustained improvement.

In summary these studies have provided valuable insights into aspects of insomnia that have direct relevance for treatment in the future. Future work planned is a controlled trial of trazodone in primary insomnia and the collection of further data from patients completing the insomnia group programme with data at follow up visits to monitor if improvement is sustained. It is also hoped to use the group to support people with chronic insomnia to decrease or cease their hypnotic medication.

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APPENDIX 1

Establishing an optimal sleep pattern

1) Go to bed only when you are **'sleepy tired'** - between 10:00pm and midnight.

2) Set a **threshold time** after which you should monitor sleepiness. The difference between this and waking time should equate to typical mean length of sleep.

3) Put the **light out** immediately you retire.

4) Do not read or watch television in bed: these are **waking** activities.

5) If you are not asleep within **20 minutes** get out of bed and sit and relax in another room until you are 'sleepy tired' again.

6) **Repeat step (5)** as often as is required, and also if you have any long awakenings in the night.

7) Set the alarm to the **same ringing time** every day. This 'anchor' should reflect your daytime/waking schedule.

8) **Do not nap** during the day.

9) **Do not take recovery sleep** to compensate for a previous bad night.

10) Follow the programme **rigidly** for several weeks to establish an efficient and regular pattern.

Also:

- Take regular **exercise** but no later than late in the afternoon
- **Cut out caffeine completely**; i.e. tea, coffee, cola.

(SleepOpt - After Espie, in Shapiro 1993)

Rehearsal and planning sessions

1) Set aside 20 minutes in the early evening, perhaps after your meal.

2) Sit in a quiet place. Have a pencil and notebook to hand.

3) Treat this time as the pivotal point between daytime activities and the evening time.

4) Reflect on the past day. Consider your achievements in relation to objectives. Encourage yourself with achievements.

5) Consider any problem areas or loose ends. Reallocate time to deal with these things. Do not do the actual work needed, but note the decisions reached.

6) Consider also any other matters which may intrude on the sleep period - for example, emotional, financial, or other worries. Write down the first or next positive step of action to take and when you will take it.

7) If when you are in bed, you start to think about any of these issues, remind yourself that you have already dealt with them and have made (and recorded) your plans so that you do not need to think about them now. If new thoughts intrude 'refer' them on to the next day. Think instead of something more pleasant: you can *choose* what you think about.

(SleepPlan - from Espie, in Shapiro 1993)

Dealing with tension and developing relaxation skills

1) **Wind down** during the second half of the evening. The body requires rest as well as sleep.

2) Set a work/activity **deadline** at least 90 minutes before your usual bedtime.

3) Practise a **relaxation routine** when in bed.

- Concentrate on breathing. Try to breathe deeply and slowly. Rehearse subvocally 'in' and 'out' to respiration.
- Tense and relax major muscle groups in turn interspersed with breathing exercises. Muscle groups comprise arms neck and shoulders; face and eyes; stomach and back; legs.
- Take the exercises slowly. Do not overtense muscles. Relaxation is about 'letting go'.

4) Practise the relaxation routine at other times during the day. Try to develop this as a **skill.**

(SleepRtxn - from Espie, in Shapiro 1993)

Sleep scheduling

1) Using your sleep diary, calculate your sleep efficiency:

- Time asleep + Time in bed x 100

- For example, if you go to bed at 10 o'clock and get up at 8 o'clock and sleep, on average, for a total of 5½ hours, your efficiency is:

- 5.5 + 10 x 100 = 55%

2) Aim to spend in bed only the amount of time that you usually sleep (but not less than five hours):

- So, if you typically sleep for 5½ hours and need to get up at 7:30am you should not go to bed until 2 o'clock in the morning however tired you are. On the other hand, if you prefer go to bed at midnight, you should get up at 5:30am.

3) Set an alarm clock for your selected getting up time.

4) Get out of bed when the alarm goes off no matter how tired you feel.

5) Do not sleep during the day. Go to bed at the same time each night.

6) Stick *rigidly* to this routine.

7) Your sleep efficiency may remain the same or decrease at first which is why this is a difficult strategy. When your sleep starts to increase you can increase the time spent in bed by 15 minutes a night. When your sleep efficiency increases again, add another 15 minutes but do not increase your time in bed more than once in a week; give yourself time to adjust.

Dealing with frustration or racing thoughts

1) Do not try too hard to fall asleep.

2) State to yourself that 'sleep will come when it is ready': that 'relaxing in bed is almost as good'.

3) Try to keep your eyes open in the darkened room and as they (naturally) try to close tell yourself to 'resist that for just another few seconds'. This procedure 'tempts' sleep to take over.

4) Try to ignore irrelevant ideas and thoughts.

5) Visualise a pleasing scene or try repeating a semantically neutral word (such as '*the*') subvocally every few seconds.

(SlpThght from Espie, in Shapiro 1993;

APPENDIX 2

THE HAMILTON RATING SCALE FOR DEPRESSION (HAMD)

(to be administered by a healthcare professional)

To rate the severity of depression in patients who are already diagnosed as depressed, administer this questionnaire. The higher the score, the more severe the depression.

For each item, write the correct number on the line next to the item. (Only one response per item)

1. **DEPRESSED MOOD** (Sadness, hopeless, helpless, worthless)
   0=Absent
_____ **1**=These feeling states indicated only on questioning
   2=These feeling states spontaneously reported verbally
   3=Communicates feeling states non-verbally – i.e., through facial expression, posture, voice, and tendency to weep
   4=Patient reports VIRTUALLY ONLY these feeling states in his spontaneous verbal and non-verbal communication

2. **FEELINGS OF GUILT**
   0=Absent
_____ **1**=Self reproach, feels he has let people down
   2=Ideas of guilt or rumination over past errors or sinful deeds
   3=Present illness is a punishment. Delusions of guilt
   4=Hears accusatory or denunciatory voices and/or experiences threatening visual hallucinations

3. **SUICIDE**
   0=Absent
_____ **1**=Feels life is not worth living
   2=Wishes he were dead or any thoughts of possible death to self
   3=Suicidal ideas or gesture
   4=Attempts at suicide (any serious attempt rates 4)

4. **INSOMNIA EARLY**
   0=No difficulty falling asleep
_____ **1**=Complains of occasional difficulty falling asleep – i.e., more than ½ hour
   2=Complains of nightly difficulty falling asleep

5. **INSOMNIA MIDDLE**
   0=No difficulty
_____ **1**=Patient complains of being restless and disturbed during the night
   2=Waking during the night – any getting out of bed rates 2 (except for purposes of voiding)

6. INSOMNIA LATE

0=No difficulty
1=Waking in early hours of the morning but goes back to sleep
2=Unable to fall asleep again if he gets out of bed

7. WORK AND ACTIVITIES

0=No difficulty
1=Thoughts and feelings of incapacity, fatigue or weakness related to activities; work or hobbies
2=Loss of interest in activity; hobbies or work – either directly reported by patient, or indirect in listlessness, indecision and vacillation (feels he has to push self to work or activities)
3=Decrease in actual time spent in activities or decrease in productivity
4=Stopped working because of present illness

8. RETARDATION: PSYCHOMOTOR (Slowness of thought and speech; impaired ability to concentrate; decreased motor activity)

0=Normal speech and thought
1=Slight retardation at interview
2=Obvious retardation at interview
3=Interview difficult
4=Complete stupor

9. AGITATION

0=None
1=Fidgetiness
2=Playing with hands, hair etc.
3=Moving about, can't sit still
4=Hand wringing, nail biting, hair-pulling, biting of lips

10. ANXIETY (PSYCHOLOGICAL)

0=No difficulty
1=Subjective tension and irritability
2=Worrying about minor matters
3=Apprehensive attitude apparent in face or speech
4=Fears expressed without questioning

11. ANXIETY SOMATIC: Physiological concomitants of anxiety, (i.e., effects of autonomic overactivity, "butterflies", indigestion, stomach cramps, belching, diarrhoea, palpitations, hyperventilation, paraesthesia, sweating, flushing, tremor, headache, urinary frequency). Avoid asking about possible medication side effects (i.e. dry mouth, constipation)

0=Absent
1=Mild
2=Moderate
3=Severe
4=Incapacitating

12. SOMATIC SYMPTOMS (GASTROINTESTINAL)

0=None

_____ **1**=Loss of appetite but eating without encouragement from others. Food intake about normal

2=Difficulty eating without urging from others

13. SOMATIC SYMPTOMS GENERAL

0=None

_____ **1**=Heaviness in limbs, back or head. Backaches, headache, muscle aches. Loss of energy and fatigability

2=Difficulty eating without urging from others

14. GENITAL SYMPTOMS (Symptoms such as: loss of libido; impaired sexual performance; menstrual disturbances)

_____ **0**=Absent

1=Mild

2=Severe

15. HYPOCHONDRIASIS

0=Not Present

_____ **1**=Self-absorption (bodily)

2=Preoccupation with health

3=Frequent complaints, requests for help, etc.

4=Hypochondriacal delusions

16. LOSS OF WEIGHT

A: When rating by history:

_____ **0**=No weight loss

1=Mild

2=Moderate

3=Severe

17. INSIGHT

0=Acknowledges being depressed and ill

_____ **1**=Acknowledges illness but attributes cause to bad food, climate, overwork, virus, need for rest, etc.

2=denies being ill at all

Montgomery Åsberg Depression Rating Scale (MADRS)

Montgomery SA, Asberg M. A new depression scale designed to be sensitive to change. Br J Psychiatry 1979;134:382-9.

(Circle correct response)

1 Apparent Sadness

- Representing despondency, gloom and despair (more than just transient low spirits), reflected in speech, facial expression and posture. Rate by depth, and ability to brighten up.

0 No sadness
1
2 Looks dispirited, but does brighten up without difficulty
3
4 Appears sad and unhappy most of the time
5
6 Looks miserable all the time. Extremely despondent

---

2 Reported Sadness

- Representing reports of depressed mood, regardless of whether it is reflected in appearance or not. Includes low spirits, despondence, or the feeling of being bored beyond help and without hope.
- Rate according to intensity, duration and the extent to which mood is reported to be influenced by events.

0 Occasional sadness in keeping with the circumstances
1
2 Sad or low but brightens up without difficulty
3
4 Pervasive feelings of sadness or gloominess. The mood is still influenced by external circumstances
5
6 Continuous or unvarying sadness, misery or despondency

---

3 Inner Tension

- Representing feelings of ill-defined discomfort, edginess, inner turmoil, mental tension mounting to either panic, dread or anguish.
- Rate according to intensity, frequency, duration and the extent of reassurance called for.

0 Placid. Only fleeting inner tension
1
2 Occasional feelings of edginess and ill-defined discomfort
3
4 Continuous feelings of inner tension or intermittent panic which the patient can only master with some difficulty
5
6 Unrelenting dread or anguish. Overwhelming panic.

---

4 Reduced Sleep

- Representing the experience of reduced duration of depth of sleep compared to the subject's own normal pattern when well.

0 Sleeps as usual
1
2 Slight difficulty
3
4 Sleep reduced or broken by at least two hours
5
6 Less than two or three hours sleep

---

5 Reduced Appetite

- Representing the feeling of a loss of appetite compared with when well. Rate by loss of desire for food, or the need to force oneself to eat.

0 Normal or increased appetite
1
2 Slightly reduced appetite
3
4 No appetite. Food is tasteless
5
6 Needs persuasion to eat at all

---

6 Concentration Difficulties

- Representing difficulties in collecting one's thoughts, mounting to incapacitating lack of concentration.
- Rate according to intensity, frequency, and degree of incapacity produced.

0 No difficulties in concentrating
1
2 Occasional difficulties in concentrating one's thought
3
4 Difficulties in concentrating and sustaining thought which reduces ability to read or hold a conversation
5
6 Unable to ready or converse without great difficulty

---

7 Lassitude

- Representing a difficulty getting started or slowness initiating and performing everyday activities.

0 Hardly any difficulty in getting started. No sluggishness
1
2 Difficulties in starting activities
3
4 Difficulties in starting simple routine activities which are carried out with effort
5
6 Complete lassitude. Unable to do anything without help

---

8 Inability to Feel

- Representing the subjective experience of reduced interest in the surroundings, or activities that normally give pleasure. The ability to react with adequate emotion to circumstances or people is reduced.

0 Normal interest in the surroundings and in other people
1
2 Reduced ability to enjoy unusual interests
3
4 Loss of interest in the surroundings. Loss of feelings for friends and acquaintances
5
6 The experience of being emotionally paralysed, inability to feel anger, grief or pleasure and a complete or even painful failure to feel for close relatives and friends

---

9 Pessimistic Thoughts

- Representing thoughts of guilt, inferiority, self-reproach, sinfulness, remorse and ruin.

0 No pessimistic thoughts
1
2 Fluctuating ideas of failure, self-reproach or self-deprecation
3
4 Persistent self-accusations, of definite but still rational ideas of guilt or sin. Increasingly pessimistic about the future
5
6 Delusions of ruin, remorse or unredeemable sin. Self-accusations which are absurd and unshakable

---

10 Suicidal Thoughts

- Representing the feeling that life is not worth living, that a natural death would be welcome, suicidal thoughts, and preparations for suicide.
- Suicidal attempts should not in themselves influence the rating.

0 Enjoys life or takes it as it comes
1
2 Weary of life. Only fleeting suicidal thoughts
3
4 Probably better off dead. Suicidal thoughts are common, and suicide is considered as a possible solution, but without specific plans or intention
5
6 Explicit plans for suicide when there is an opportunity. Active preparations for suicide

Patient ID: _____
Study: _____ Visit: _____

Clinical Global Impressions (CGI)

Guy W, editor. Clinical Global Impression (CGI). In: *ECDEU Assessment Manual for Psychopharmacology*. Rockville, MD: US Department of Health and Human Services, Public Health Service, Alcohol Drug Abuse and Mental Health Administration, NIMH Psychopharmacology Research Branch, 1976; 218–222.

Severity of Illness (CGI-S)

Considering your total clinical experience with this particular population, how mentally ill is the patient at this time?

0 = not assessed
1 = normal, not at all ill
2 = borderline mentally ill
3 = mildly ill
4 = moderately ill
5 = markedly ill
6 = severely ill
7 = among the most extremely ill patients

Global Improvement (CGI-I)

Rate total improvement, whether or not, in your judgement, it is entirely due to drug treatment. Compared to his condition at the end of baseline, how much has he changed?

1 = very much improved
2 = much improved
3 = minimally improved
4 = no change
5 = minimally worse
6 = much worse
7 = very much worse

Comments

Assessors Signature: _____ *Date:* _____

St. Mary's Hospital Sleep Questionnaire

This questionnaire refers to your sleep over the past 24 hours. Please try and answer every question.

Name.....Date .....

At what time did you:

1) settle down for the night?.....

2) fall asleep last night? .....

3) finally wake this morning?.....

4) get up this morning?.....

5) Was your sleep (tick box)

1 very light	⊖
2 light	⊖
3 fairly light	⊖
4 light average	⊖
5 deep average	⊖
6 fairly deep	⊖
7 deep	⊖
8 very deep	⊖

6) How many times did you wake up? (tick box)

0 not at all	⊖
1 once	⊖
2 twice	⊖
3 three times	⊖
4 four times	⊖
5 five times	⊖
6 six times	⊖
7 more than six times	⊖

How much sleep did you have

7) last night? .....hrs.....mins

8) during the day, yesterday? .....hrs.....mins

9) How well did you sleep last night? (tick box)

1 very badly ⊖
2 badly ⊖
3 fairly badly ⊖
4 fairly well ⊖
5 well ⊖
6 very well ⊖

If not well what was the trouble (eg restless, etc)?

1 _____

2 _____

3 _____

10) How clear-headed did you feel after getting up this morning? (tick box)

1 still very drowsy indeed ⊖
2 still moderately drowsy ⊖
3 still slightly drowsy ⊖
4 fairly clear-headed ⊖
5 alert ⊖
6 very alert ⊖

11) How satisfied were you with last night's sleep? (tick box)

1 very unsatisfied ⊖
2 moderately unsatisfied ⊖
3 slightly unsatisfied ⊖
4 fairly satisfied ⊖
5 completely satisfied ⊖

12) Were you troubled by waking early and being unable to get off to sleep again? (tick box)

NO ⊖ YES ⊖

13) How much difficulty did you have in getting off to sleep last night? (tick box)

1 none or very little ⊖
2 some ⊖
3 a lot ⊖
4 extreme difficulty ⊖

14) How long did it take you to fall asleep last night? ..... hrs..... mins

LEEDS SLEEP EVALUATION QUESTIONNAIRE

Subject name/initials_____ Number_____Date_____

Each question is answered by placing a vertical mark on the line. If no change was experienced then place the mark in the middle of the line. If a change was experienced then the position of your mark will indicate the nature and extent of the change ie large changes near the ends of the line, small changes near the middle.

For example, this would indicate a small change:

How would you compare getting to sleep last night with getting to sleep normally?

a) Easier than usual — Harder than usual

b) Quicker than usual — Slower than usual

c) Felt more drowsy than usual — Felt less drowsy than usual

How would you compare the quality of your sleep last night with your usual sleep?

a) More restful than usual — More restless than usual

b) Fewer periods of wakefulness than usual — More periods of wakefulness than usual

---

How did your awakening this morning compare with your usual awakening?

a) Easier than usual — Harder than usual

b) Took less time than usual — Took more time than usual

How did you feel on waking?

Alert — Tired

How do you feel now?

Alert — Tired

How was your sense of balance and coordination on waking?

Less clumsy than usual — More clumsy than usual

SLEEP DIARY Name.....

QUALITY OF MY SLEEP WAS ....

0 1 2 3 4 5 6 7 8 9 10

least refreshing ever average most refreshing ever

date	time I went to bed	time I fell asleep	time I woke up in the morning	estimate of total sleep time (hours)	number of times I woke in the night	sleep quality 0-10	Comment (stressful events, illness, medication etc)

APPENDIX 3

Chapter 3: Non significant data and graphs

Non significant Objective sleep data:

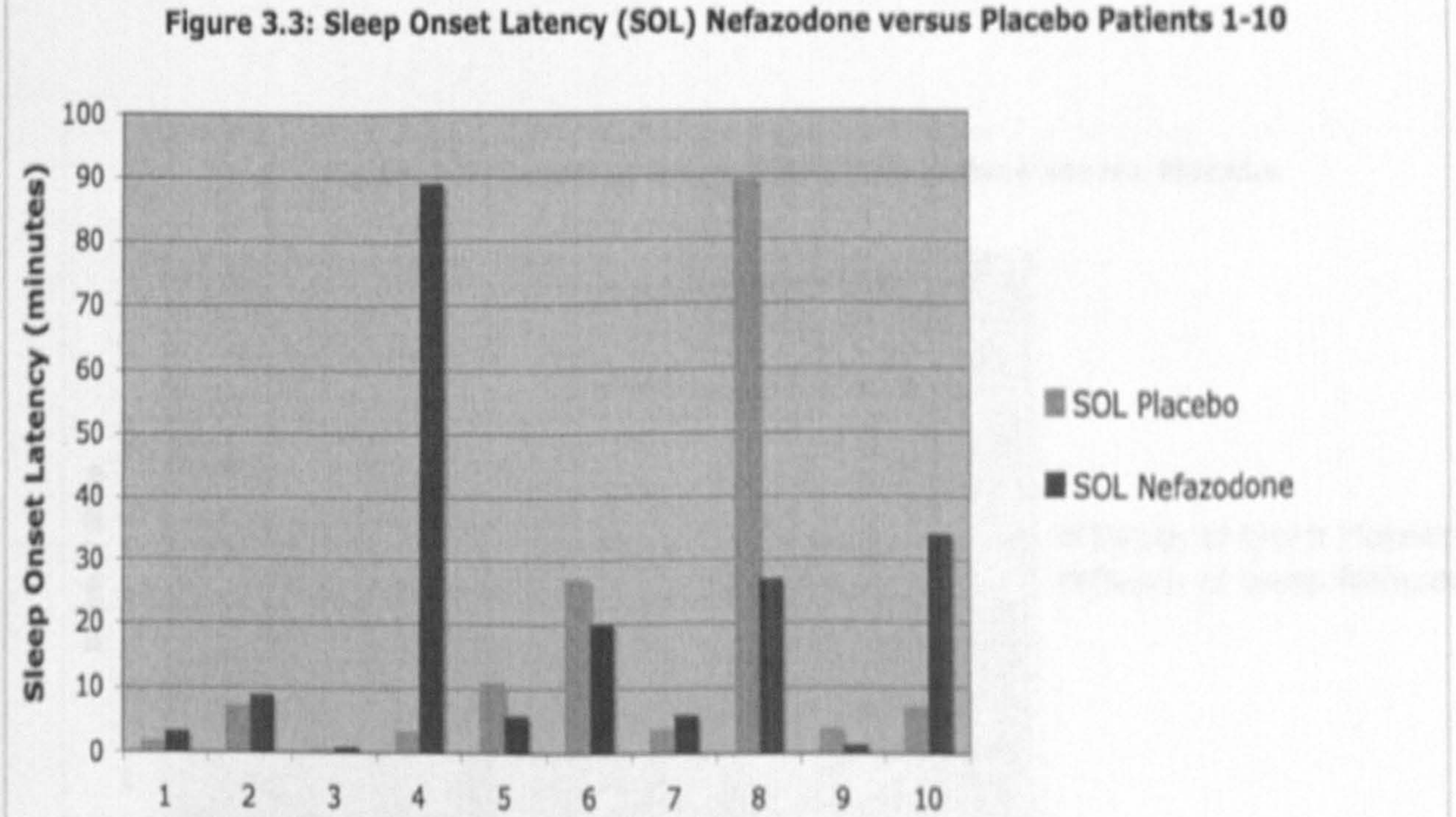
Table 3.1: Paired t test Results

Sleep Parameter	Nefazodone (Mean value for whole group) n=10	Placebo (Mean value for whole group) n=10	Mean Difference	Standard Deviation	t statistic (paired t test)	P value
stage 1(min)	43.1	37.2	5.9	16.9	1.0	ns
stage 2(min)	209.6	200.6	-8.9	52.9	-0.5	ns
stage 3(min)	27.8	21.6	-6.3	-9.9	-1.8	ns
stage 4(min)	32.9	39.4	6.5	13.5	-1.4	ns
REM sleep(min)	98.7	83.2	-15.5	33.2	-1.4	ns

Table 3.2: Wilcoxon Sign Rank Test Results

	Nefazodone (Mean value for whole group) n=10	Placebo (Mean value for whole group) n=9 except for SOL when n=10	Z value	P value
SOL(mins)	19.7	15.6	-0.4	ns
ROL(mins)	56.9	102.7	0.8	ns
WASO (mins)	49.9	68.5	1.4	ns

Figure 3.3: Sleep Onset Latency (SOL) Nefazodone versus Placebo Patients 1-10



Non significant subjective sleep data (SMHQ)

Figure 3.5: Subjective Sleep Onset Latency (SOL) SMHQ Nefazodone versus Placebo

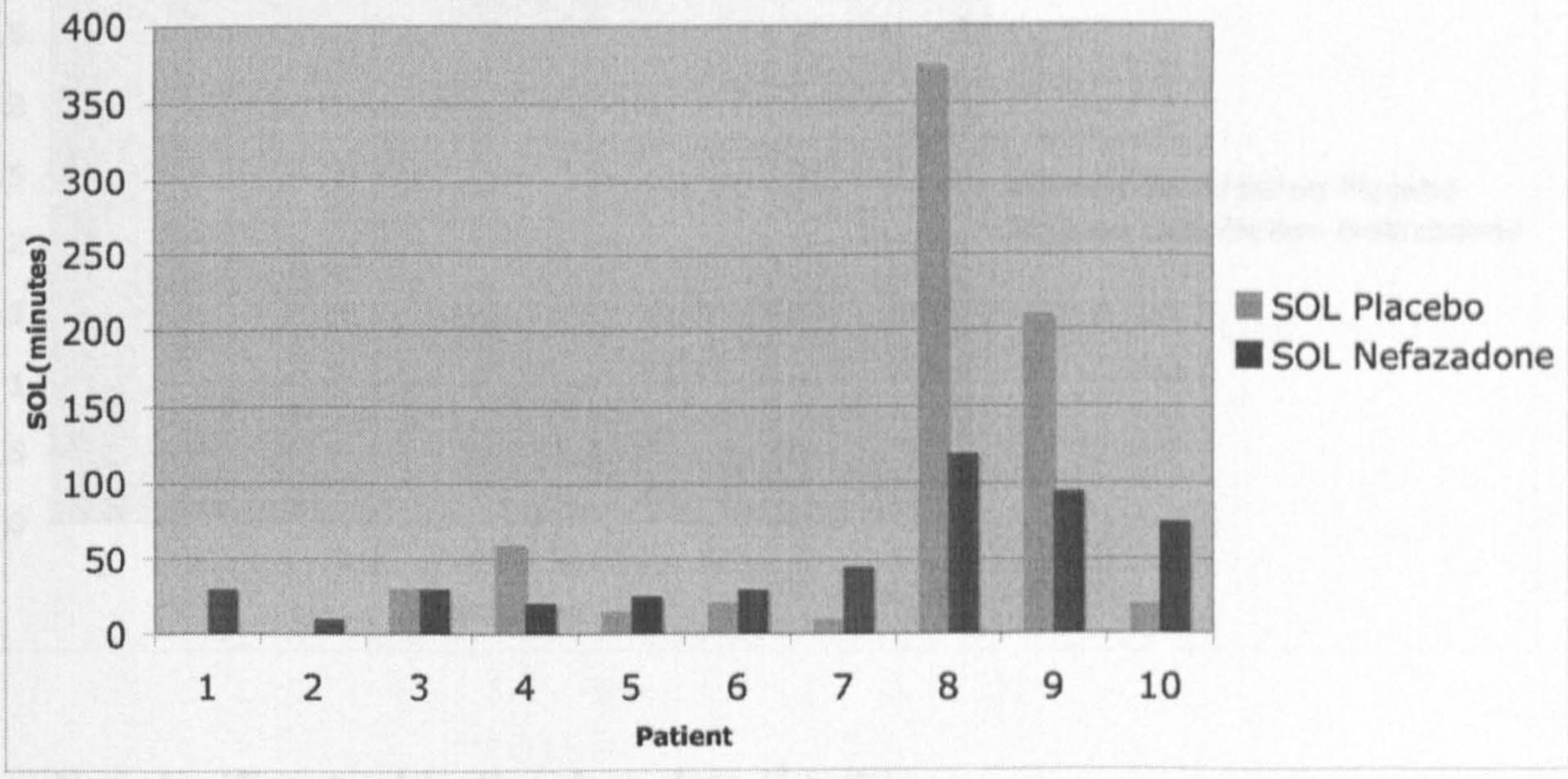


Figure 3.6: Depth of Sleep SMHQ Nefazodone versus Placebo

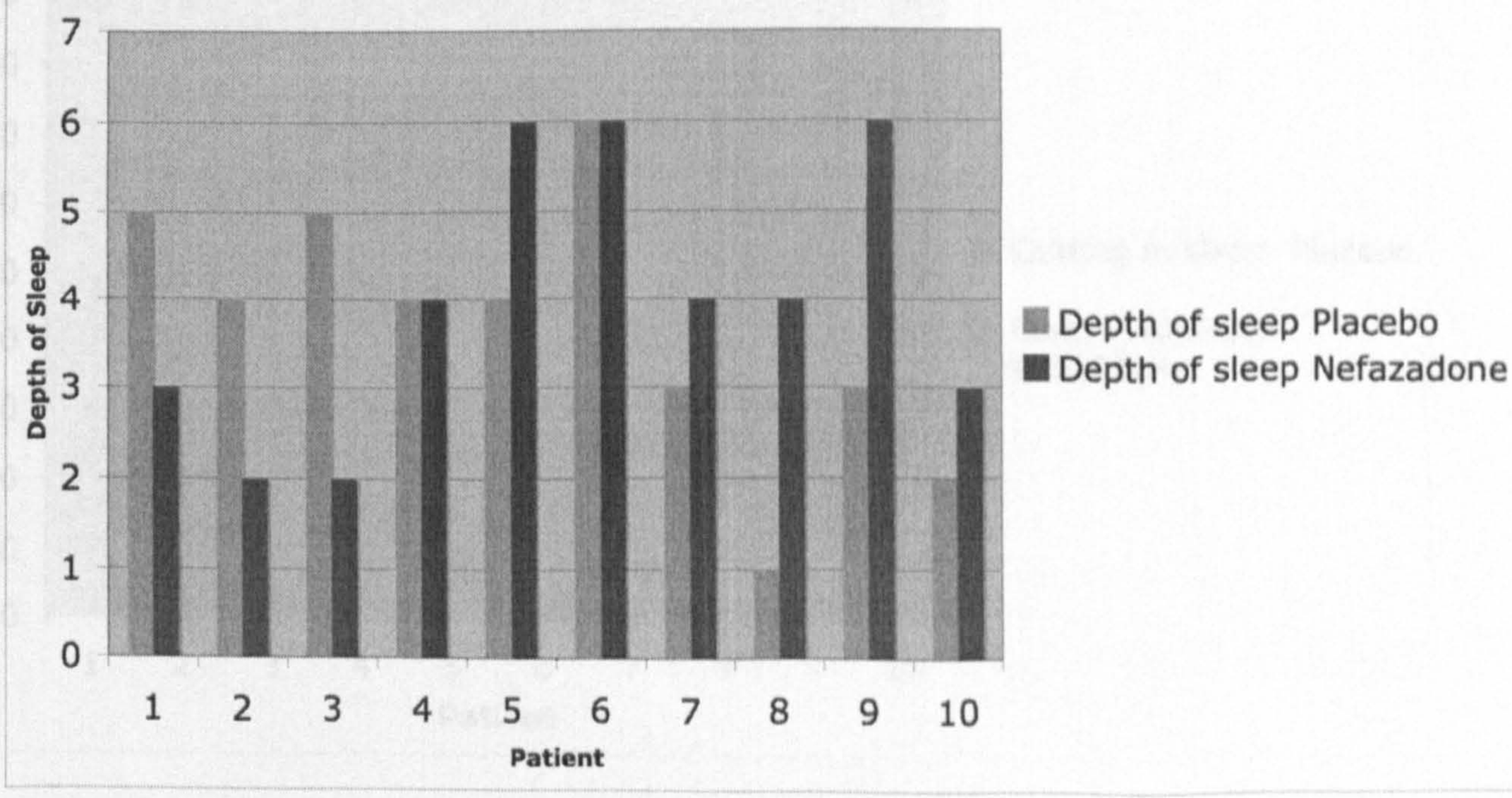
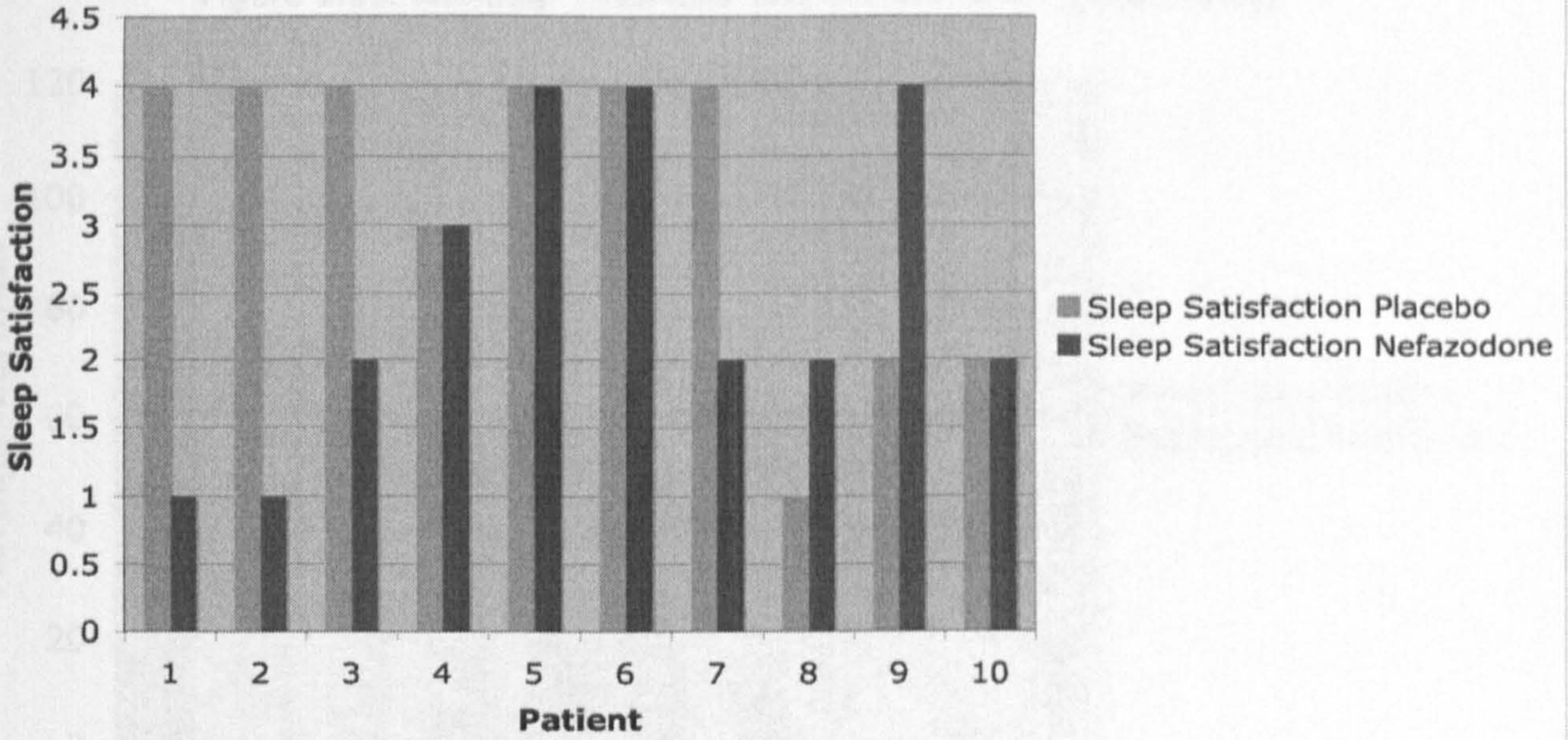


Figure 3.7: Sleep Satisfaction SMHQ Nefazodone versus Placebo



Non significant subjective sleep data (Leeds):

Figure 3.9: "Getting to Sleep" LSQ Nefazodone versus Placebo

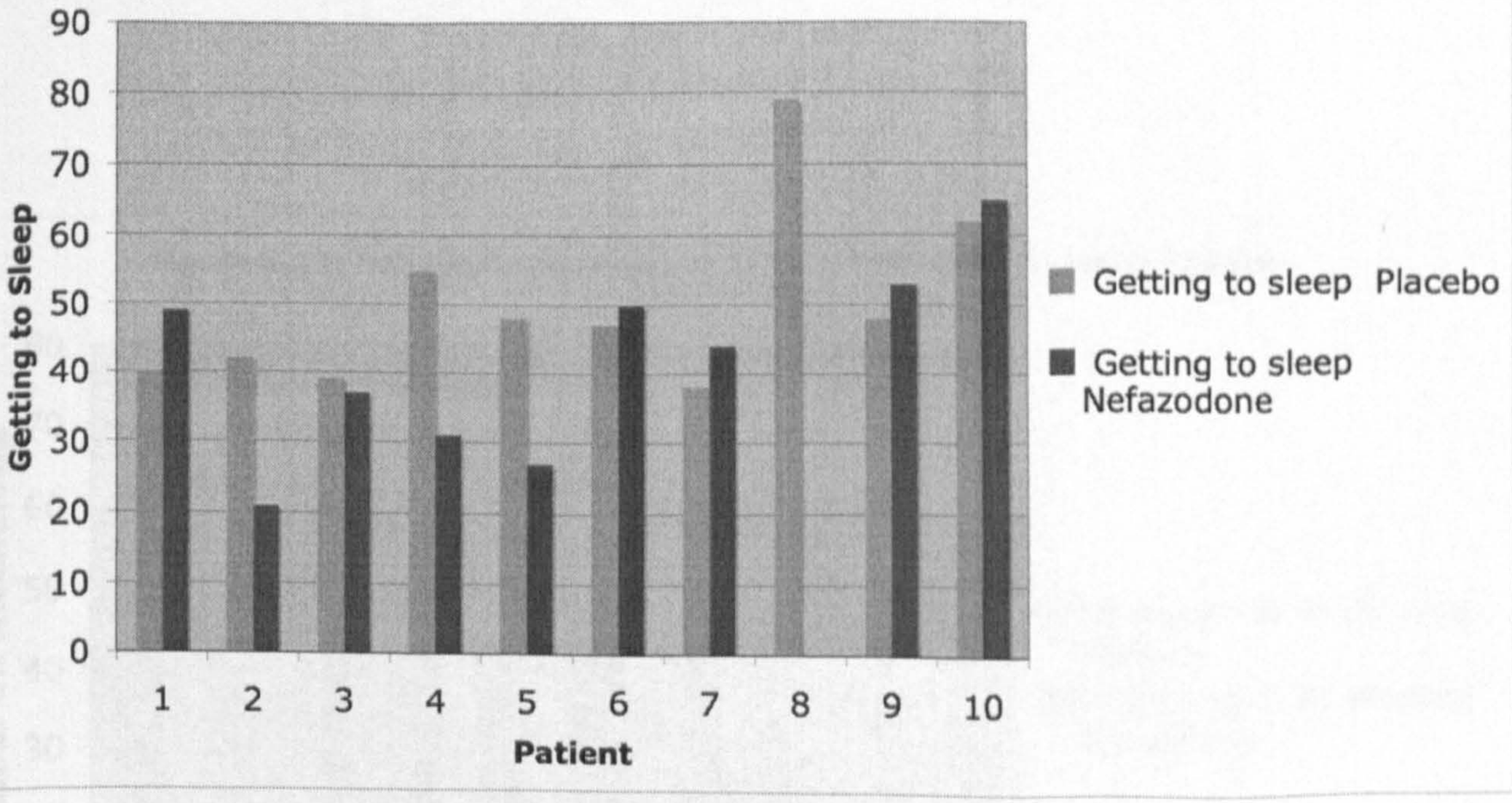


Figure 3.10: Morning Tiredness LSQ Nefazodone versus Placebo

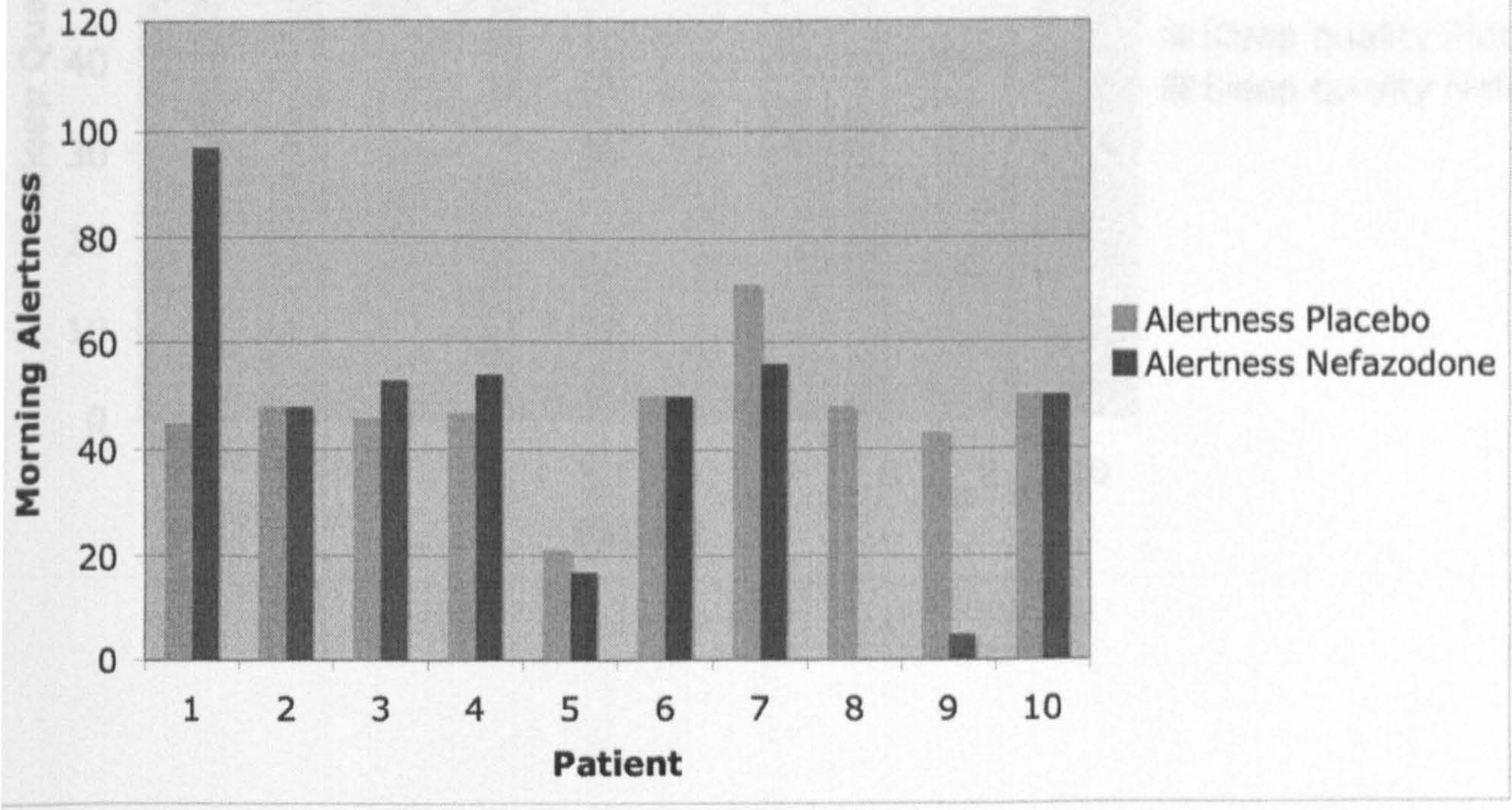


Figure 3.11: Behaviour on Awakening LSQ Nefazodone versus Placebo

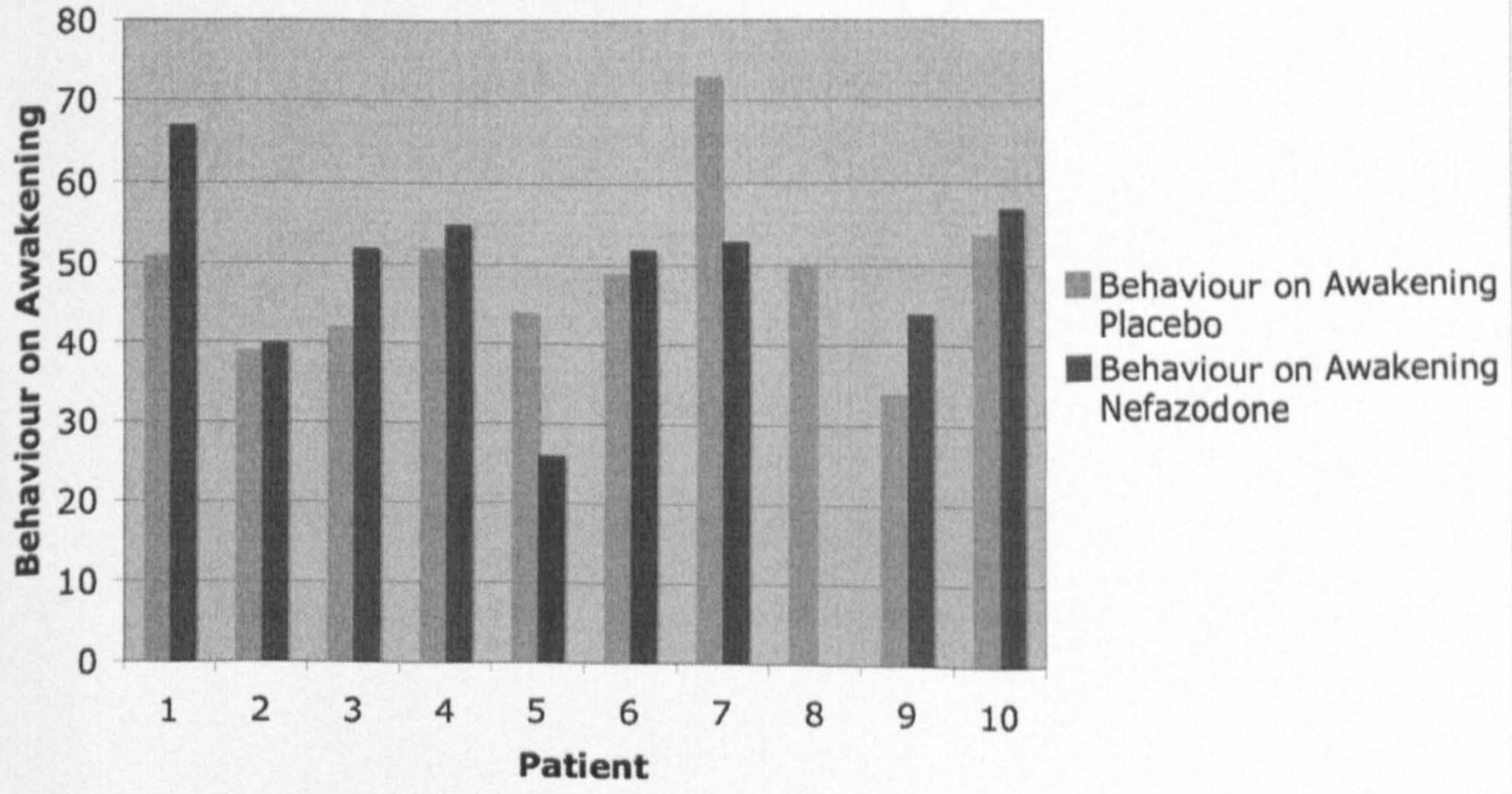
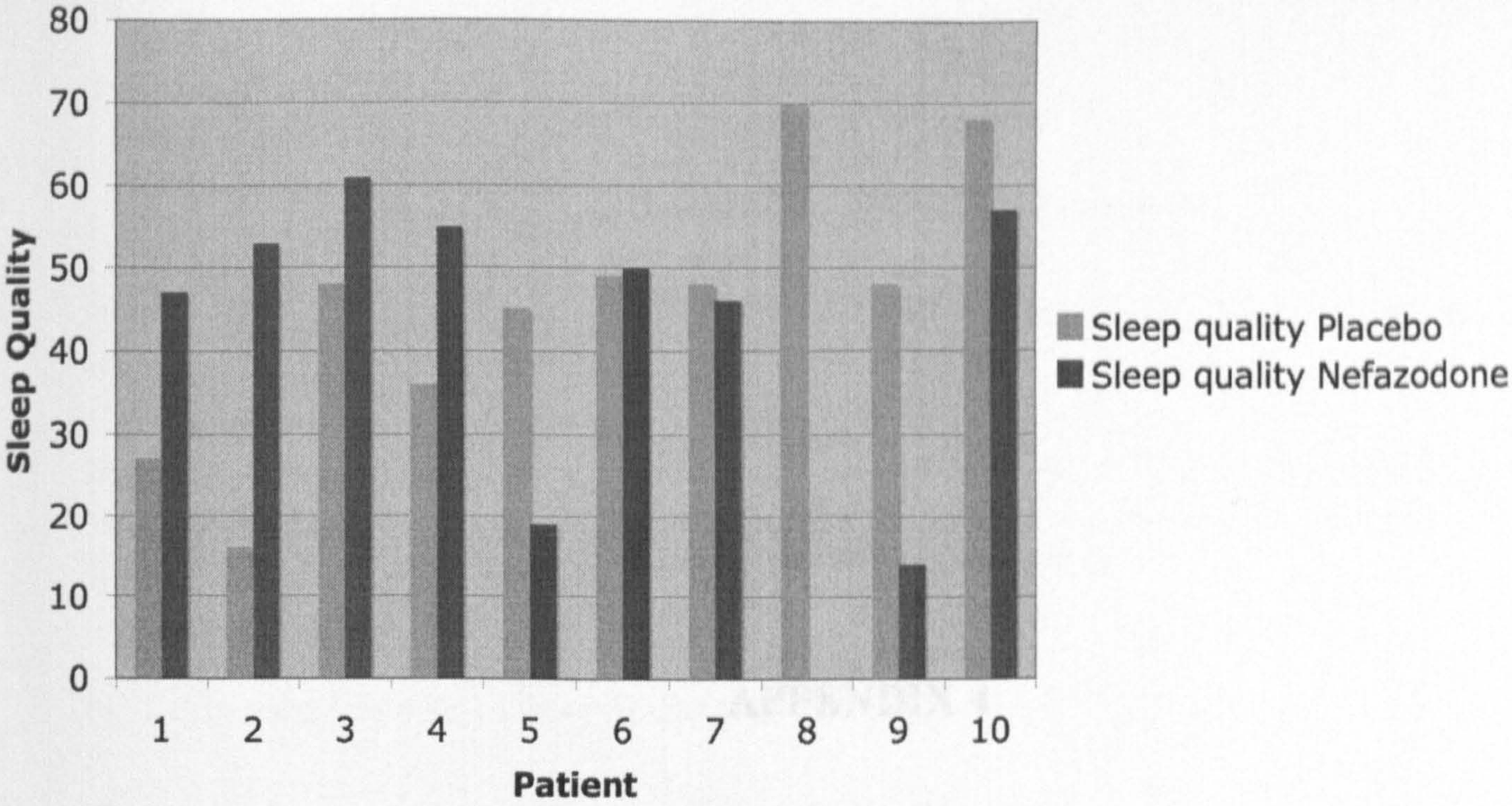


Figure 3.12: Sleep Quality LSQ Nefazodone versus Placebo



APPENDIX 4

NAME ..... Date .....

SF-36: General Health Questionnaire

This questionnaire asks for your views about your health and how well you are able to do your usual activities.

Please answer each question by circling the appropriate number 1, 2, 3, ... If you are unsure about how to answer a question, please give the best answer you can and make a comment in the **left margin** but please only circle **one** number for any question.

1. In general would you say that your health is:

(circle one number)

Excellent	1
Very good	2
Good	3
Fair	4
Poor	5

2. **Compared to one year ago**, how would you rate your general health **now**?

(circle one number)

Much better now than one year ago	1
Somewhat better now than one year ago	2
About the same	3
Somewhat worse than one year ago	4
Much worse than one year ago	5

PF	RLP	RLM	SC	MH	EV	P	HP	CIH

HEALTH AND DAILY ACTIVITIES

3. The following questions are about activities you might do during a typical day. Does your health limit you in these activities? If so, how much? (Circle 1,2, *or* 3 on each line).

	Yes limited a lot	Yes limited a little	No, not limited at all
a. Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports	1	2	3
b. Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	1	2	3
c. Lifting or carrying groceries	1	2	3
d. Climbing several flights of stairs	1	2	3
e. Climbing one flight of stairs	1	2	3
f. Bending, kneeling or stooping	1	2	3
g. Walking more than one mile	1	2	3
h. Walking half a mile	1	2	3
i. Walking 100 yards	1	2	3
j. Bathing or dressing yourself	1	2	3

4. During the **past 4 weeks**, have you had any of the following problems with your work or other regular daily activities **as a result of your physical health?** (Please answer YES *or* NO for each question by circling 1 *or* 2 on each line.)

	YES	NO
a. Cut down on the amount of time you spent on work or other activities	1	2
b. Accomplished less than you would like	1	2
c. Were limited in the kind of work or other activities	1	2
d. Had difficulty performing the work or other activities (for example, it took extra effort)	1	2

5. During the **past 4 weeks**, have you had any of the following problems with your work or other regular daily activities **as a result of any emotional problems** (such as feeling depressed or anxious)? Please answer YES *or* NO for each question by circling 1 *or* 2 on each line.)

	YES	NO
a. Cut down on the amount of time you spent on work or other activities	1	2
b. Accomplished less than you would like	1	2
c. Didn't do work or other activities as carefully as usual	1	2

6. During the **past 4 weeks**, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbours or groups?

(circle one number)

Not at all 1

Slightly 2

Moderately 3

Quite a bit 4

Extremely 5

PAIN

7. How much **bodily** pain have you had during the **past 4 weeks**?

(circle one number)

None.....1

Very mild 2

Mild 3

Moderate 4

Severe 5

Very severe 6

8. During the **past 4 weeks**, how much did **pain** interfere with your normal work (including work both outside the home and housework)

(circle one number)

Not at all 1

A little bit 2

Moderately 3

Quite a bit 4

Extremely 5

YOUR FEELINGS

9. These questions are about how you feel and how things have been with you **during the past month**. For each question, please indicate one answer that comes closest to the way you have been feeling.

How much of the time during the **past month** ...

(circle one number on each line)

	All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	None of the time
a. Did you feel full of life?	1	2	3	4	5	6
b. Have you been a very nervous person?	1	2	3	4	5	6
c. Have you felt so down in the dumps that nothing could cheer you up?	1	2	3	4	5	6
d. Have you felt calm and peaceful?	1	2	3	4	5	6
e. Did you have a lot of energy?	1	2	3	4	5	6
f. Have you felt downhearted and low?	1	2	3	4	5	6
g. Did you feel worn out?	1	2	3	4	5	6
h. Have you been a happy person?	1	2	3	4	5	6
i. Did you feel tired?	1	2	3	4	5	6
j. Has your health limited your social activities (like visiting friends or close relatives)?	1	2	3	4	5	6

10. Please choose the answer that best describes how **true** or **false** each of the following statements is for you.

(circle one number on each line)

	Definitely true	Mostly true	Not sure	Mostly false	Definitely false
a. I seem to get ill more easily than other people.	1	2	3	4	5
b. I am as healthy as anybody I know.	1	2	3	4	5
c. I expect my health to get worse.	1	2	3	4	5
d. My health is excellent.	1	2	3	4	5

THANK YOU FOR COMPLETING THIS QUESTIONNAIRE

PLEASE TAKE A MOMENT TO CHECK THAT YOU HAVE COMPLETED ALL OF THE QUESTIONS ON ALL 6 PAGES

Personal beliefs and attitudes about sleep

Name.....

Group [ ] Date .....

Some statements about people's beliefs and attitudes about sleep are listed below. Please indicate to what extent you personally agree or disagree with each statement. There is no right or wrong answer. For each statement, place a mark (/) along the line wherever your personal rating falls. Try to use the whole scale rather than placing your marks at one end. Please answer all the questions even if you do not have a sleep problem.

1. I need 8 hours sleep to feel refreshed and function well during the day.

STRONGLY DISAGREE ——— STRONGLY AGREE

2. When I don't get proper amount of sleep on a given night, I must catch up next day by napping or on the next night by sleeping longer.

STRONGLY DISAGREE ——— STRONGLY AGREE

3. Because I am getting older, I need less sleep.

STRONGLY DISAGREE ——— STRONGLY AGREE

4. I am worried that if I go for 1 or 2 nights without sleep, I may have a 'nervous breakdown'.

STRONGLY DISAGREE ——— STRONGLY AGREE

5. I am concerned that chronic insomnia may have serious consequences on my physical health.

STRONGLY DISAGREE ——— STRONGLY AGREE

6. By spending more time in bed, I usually get more sleep and feel better next day.

STRONGLY DISAGREE ——— STRONGLY AGREE

7. When I have trouble falling asleep or getting back to sleep after night-time awakening, I should stay in bed longer and try harder.

STRONGLY DISAGREE ——— STRONGLY AGREE

8. I am worried that I may lose control over my ability to sleep.

STRONGLY DISAGREE ——— STRONGLY AGREE

9. Because I am getting older I should go to bed earlier in the evening.

STRONGLY DISAGREE ——— STRONGLY AGREE

10. After a poor night's sleep I know that it will interfere with my daily activities on the next day.

STRONGLY DISAGREE ——— STRONGLY AGREE

11. To be alert and function well during the day, I believe I would be better off taking a sleeping pill rather than having a poor night's sleep.

STRONGLY DISAGREE ——— STRONGLY AGREE

12. When I feel irritable, depressed or anxious during the day, it is mostly because I did not sleep well the night before.

STRONGLY DISAGREE ——— STRONGLY AGREE

13. Because my bed-partner falls asleep as soon as his/her head hits the pillow and stays asleep during the night, I should be able to do so too.

STRONGLY DISAGREE ——— STRONGLY AGREE

PLEASE TURN OVER

APPENDIX 5

BRITISH JOURNAL OF PSYCHIATRY (2002), 180, 528–535

Randomised controlled study of sleep after nefazodone or paroxetine treatment in out-patients with depression

J. A. HICKS, S. V. ARGYROPOULOS, A. S. RICH, J. R. NASH, C. J. BELL, C. EDWARDS, D. J. NUTT and S. J. WILSON

Background Sleep effects of antidepressants are important clinically and for elucidating mechanism of action: selective serotonin reuptake inhibitors disturb sleep and 5-HT_2 receptor-blocking compounds may enhance sleep quality.

Aims To compare the objective and subjective effects on sleep of paroxetine and nefazodone in patients with moderate to severe depression.

Method Forty patients with depression were randomised to take paroxetine 20–40 mg/day or nefazodone 400–600 mg/day for 8 weeks. Objective and subjective quality of sleep and depression measures were assessed throughout.

Results Nefazodone significantly increased objective sleep efficiency and total sleep time, and improved subjective sleep on days 3 and 10. Paroxetine decreased sleep efficiency early in treatment and some sleep disruption remained at week 8. Paroxetine but not nefazodone produced marked suppression of rapid eye movement (REM) sleep.

Conclusions Nefazodone improves sleep in early treatment compared with paroxetine in patients with moderate to severe depression. These effects are seen within the first 2 weeks of treatment and diminish thereafter.

Declaration of interest Funding and medication were provided by Bristol-Myers Squibb Pharmaceuticals, UK.

The efficacy of new antidepressants introduced in recent years generally appears to be equal to that of the established classes of drugs, particularly the tricyclics (TCAs) and the selective serotonin reuptake inhibitors (SSRIs) (Anderson *et al*, 2000). However, some new compounds claim advantages over other agents, especially the SSRIs. These advantages, which differ from drug to drug, either refer to specific side-effects, such as sexual dysfunction, or to symptoms of the depressive illness that are not adequately controlled by the SSRIs, such as sleep. Nevertheless, head-to-head comparisons between the new agents and the SSRIs, designed specifically to test these claims, are still scarce.

Antidepressants and sleep

One of the new compounds, nefazodone, is said to confer an advantage over the SSRIs in improving sleep, even before the onset of antidepressant action. This clinically useful characteristic is shared with the TCAs but the latter group, unlike nefazodone, is handicapped by danger in overdose and troublesome anticholinergic side-effects. By contrast, the SSRIs are not considered sleep-promoting. Disturbed sleep is one of the most frequent and distressing symptoms in moderate and severe depression. Objective sleep changes in depression include shortened rapid eye movement (REM) latency, disruption of sleep continuity, early morning waking and reduction of slow wave sleep, particularly in the first sleep cycle (Benca *et al*, 1992). Antidepressants such as the TCAs and SSRIs produce marked suppression of REM sleep. The TCAs tend to improve sleep fragmentation acutely whereas SSRIs decrease sleep continuity until there is resolution because of improvement of the depressive illness (Wilson *et al*, 2000).

Nefazodone weakly antagonises the reuptake of serotonin (5-HT) and noradrenaline (Tatsumi *et al*, 1997); it also blocks the post-synaptic 5-HT_2 receptor and the α_1-adrenoceptor, but does not block histamine or cholinergic receptors, the supposed mechanism producing the sedative effects of TCAs (Cusack *et al*, 1994). In a multi-centre sleep laboratory study in major depression (Rush *et al*, 1998) nefazodone improved sleep over an 8-week period compared with fluoxetine. No study, however, has looked at the first 2 weeks of treatment or at patients sleeping in their home environment.

METHOD

Protocol and study objectives

This was a single-site, double-blind, randomised, parallel-group, 8-week study of sleep in patients with moderate to severe depression without psychotic features. The objective of this trial was to compare the effects of nefazodone and paroxetine on sleep and mood. The study was approved by the local ethics committee and all patients gave written informed consent. At the end of the acute phase of the treatment (8 weeks) patients who showed at least minimal improvement on the Clinical Global Impression (CGI) Improvement scale (Guy, 1976) continued to be studied clinically, but without sleep measures, for a further 16 weeks.

Patient population

Consecutive referrals to a hospital psychiatric out-patient clinic and direct referrals from two general practices were assessed for eligibility in the study. They were screened with full medical and psychiatric history, mental state examination and physical examination. To be randomised into the study, patients had to fulfil diagnostic criteria for DSM–IV (American Psychiatric Association, 1994) moderate to severe depression, scoring 18 or over on the Hamilton Rating Scale for Depression (HRSD; Hamilton, 1960). Exclusion criteria included schizophrenia, history of mania, active suicidal ideation, alcohol misuse and illicit drug use. Patients unable to maintain a consistent sleep pattern, such as shift workers or those with a current sleep/wake disorder, were also excluded. Pre-menopausal women were required to have a negative pregnancy test at screening and to take precautions against pregnancy during the trial. Subjects who had previously taken psychoactive medication including benzodiazepines were required

to undergo a 2-week (or 5-week in the case of fluoxetine) washout period before entering the trial. In the event, six of the patients had received benzodiazepines, none in the previous year, and four patients had received fluoxetine in the previous year, one stopping for the study.

Patients who had received any other investigational drug up to 30 days before the initiation of therapy, or who were participating in another clinical study at the time of the assessment, were not considered for inclusion in this protocol. Pregnant or nursing females, or women of childbearing potential who were not using adequate methods of birth control were also excluded.

Determination of sample size

This was calculated to detect the smallest clinically relevant differences in two sleep parameters measured by electroencephalogram (EEG) (total sleep time and number of awakenings) with an 80% power (P=0.05) based on variance data from a previous sleep study conducted in our laboratory (Wilson *et al*, 2000), and the two-sample method (Gore & Altman, 1982) was applied. The estimated sample size was 18 patients in each group providing valid data for at least three sleep assessment days (see later). The target sample size was then extended to 22, to allow for dropouts. In the event of the study, fewer dropouts occurred than had been anticipated.

Study design and medication

Forty patients were randomly assigned on day 1 of the study, after the baseline period, to receive either nefazodone or paroxetine. Randomisation was carried out by Bristol-Myers Squibb, in blocks of four, so that in any one block there were two patients taking nefazodone and two taking paroxetine. All study medication was re-encapsulated. Capsules and container bottles were identical in shape, but of two different colours. Medication was provided for an extra 3 days a week, to allow for late follow-up visits. Treatment was taken in a twice daily regimen by mouth, with patients taking one or two capsules from the nefazodone/placebo bottle twice a day and a capsule from the paroxetine/placebo bottle in the morning. Patients commenced on day 1 with either morning nefazodone (100 mg twice daily), evening nefazodone (100 mg+placebo) or morning paroxetine (20 mg+placebo), evening placebo. After 1 week, the dose of nefazodone was increased to 200 mg twice daily and that of paroxetine remained at 20 mg once a day. Further titration was according to clinical response and side-effects, and occurred during scheduled visits or urgent visits if there were any problems. Adverse events were monitored specifically from a checklist of 95 symptoms and recorded during each visit. Patients also had 24-h telephone access to an investigator if anything untoward occurred. The patients were instructed to return all unused medication in the original package at each visit. No additional psychoactive medication was allowed during the washout and treatment phase of the study. Wherever possible, all other non-psychotropic concomitant medications and non-pharmacological therapies were recorded and kept constant for the duration of the study.

Assessments

At baseline, a physical examination was performed; vital signs (pulse, blood pressure) were recorded, and demographic data were collected. Information about previous episodes of depression was obtained from case notes and patients' and relatives' recollection. A pregnancy test was performed as indicated above. A baseline EEG was performed using the home ambulatory monitoring system (Medilog, Oxford Instruments Medical, Old Woking). Subjects were visited in their homes during the evening and the recording equipment for electroencephalography, electro-oculography and electromyography was attached, according to the standard sleep montage (Rechtschaffen & Kales, 1968). The subjects were then left to sleep normally at home. They were asked not to bathe or shower with the equipment on but told that otherwise they could carry out their normal domestic routine; they were asked not to drink alcohol for the 48 h before the recording but were allowed their normal caffeine intake. They were instructed to keep to their normal bedtime routine and to press the event marker on the recorder when they turned out the lights and tried to sleep, and on waking finally the following morning. Subjective measures of sleep using the St Mary's Hospital Sleep Questionnaire (SMHSQ; Leigh *et al*, 1988) were obtained on the morning after the recording. Thereafter sleep recordings and subjective sleep questionnaires (SMHSQ and Leeds Sleep Evaluation Questionnaire (LSEQ; Parrott & Hindmarch, 1978)) were performed at days 3 and 10 and week 8 of treatment. Patients kept a diary of sleep quality and number of awakenings for the first 21 days of treatment.

Sleep analysis

Sleep was scored automatically by the Medilog 9002 with visual correction by an experienced sleep scorer (J.A.H.) according to the Rechtshaffen & Kales (1968) criteria. The following parameters were derived from the sleep recordings. (a) Staging time – the interval between the patient pressing the event markers (when these were omitted, the sleep scorer judged these times from the EEG recording when the patient closed their eyes at night and when they opened them and started to move around in the morning). (b) Total sleep time (TST) – time in all stages of sleep. (c) Sleep efficiency – %TST/staging time. (d) Number of awakenings – these had to be greater than 16 s in duration. (e) Sleep onset latency – time from the patient pushing the button to start their night's sleep to the first 2 min of stage 2 sleep. (f) Duration of stage 1–4, and REM sleep and REM onset latency – the time to the first continuous 2 min of REM from the onset of stage 2 sleep. (g) Wakefulness after sleep onset – total time spent awake after sleep onset.

Efficacy of the antidepressant treatment was measured with the HRSD (Hamilton, 1960), Montgomery–Åsberg Depression Rating Scale (MADRS; Montgomery & Åsberg, 1979) and CGI Severity and Improvement scales (Guy, 1976). These were completed by the clinician at baseline, days 3 and 10, and at the end of weeks 3, 4, 6, 8, 16 and 24 (end of study) or at any point that a patient was prematurely withdrawn from the study.

Statistical analysis

Statistical analysis of objective sleep measures was carried out using STATA version 5.0 for Windows (STATA Corporation). Descriptive statistics were derived for each of the variables. Tests for normality showed that the variables stage 1, stage 3, sleep onset latency, REM onset latency and wakefulness after sleep onset

were not normally distributed. The values for stage 1 sleep and sleep onset latency and wakefulness after sleep onset were normalised by logarithmic transformation, and those for stage 3 sleep, REM onset latency and wakefulness after sleep onset, by square root transformation. Complete data-sets (four sleep assessments) were available for 29 individuals and this resulted in an unbalanced design. Consequently, a sequential fitting of the different sum of squares was used. Split plot analysis of variance (split plot ANOVA) was used to investigate the effects of the two drugs on all the sleep variables. This analysis separates the variance ascribable to pre-treatment differences between the two treatment groups, resulting from the effect of time, the interaction between time and treatment and the effect of the treatments themselves.

Data from HRSD, MADRS and CGI severity and improvement scales were tabulated using both the observed values and with last observation carried forward (LOCF) in the whole (intent to treat; ITT) group. Number of responders (50% or more reduction on baseline HRSD) and remitters (HRSD $\leqslant 8$) were tabulated for each treatment group. Total scores for the rating scales were analysed using ANOVA, first at baseline and on the change from baseline at the end of the specific weeks and endpoint (subject's last available observation).

Descriptive statistics, comparison tests at days 3, 10 and week 8 and ANOVA were performed on the scores of LSEQ, the items 5, 6, 9–11 and 13 of SMHSQ and the sleep items of HRSD. Values from the daily diary of sleep quality were analysed with descriptive statistics and scrutinised for possible trends in the data. An average score for each week of the study was compared for the two groups.

Adverse events were cross-tabulated by treatment, severity and clinical estimate of relation to study medication, to detect any evidence of drug-related trends or increased incidence.

All statistical tests and analysis of subjective and mood measures were performed using the standard SPSS package (version 10.0 for Windows).

RESULTS

Participant recruitment and follow-up

Forty patients (23 females, 17 males) were randomised to nefazodone (n=20) or paroxetine (n=20). Demographic data and past psychiatric history data, including comorbidity, are presented in Table 1. There were no significant differences between the groups in these variables. The number of patients that completed the study and the reasons for early discontinuation are presented in Table 2.

Patients excluded from the sleep analysis were: one patient who completed baseline only; one patient who completed baseline and day 3, but day 10 recording was technically unsatisfactory; and one patient whose baseline recording was technically unsatisfactory. One other patient's day 3 recording was technically unsatisfactory but baseline, day 10 and week 8 were included, and six other patients had no week 8 recording as they left the study.

The mean nefazodone dose (and standard deviation (s.d.)) used in the study was 495 mg/day (82.6) and for paroxetine it was 29.5 mg/day (8.9), well within the therapeutic range advised for these drugs in the treatment of depression.

Analysis of sleep

In the paroxetine group, four patients at day 3 and one patient at day 10 had no REM sleep at all. In these patients the REM latency was taken to be the staging time minus sleep onset latency.

Table 3 shows polysomnographic data of sleep parameters with results of ANOVA statistical analysis.

There were significant pre-treatment differences between the two treatment groups on nearly all the sleep measures, with sleep in the paroxetine group being generally worse. This occurred entirely by chance, as allocation was random. As

Table 1 Baseline demographic and clinical data

Baseline characteristic	Nefazodone (n=20)	Paroxetine (n=20)
Age (years) (mean, s.d.)	42.75 (11.93)	42.95 (10.12)
Median (range)	46 (18–62)	44.5 (23–59)
Gender (% male)	8 (40)	9 (45)
Women (%)	12 (60)	11 (55)
Past history of depression (%)	12 (60)	11 (55)
Previous antidepressants (%)	16 (80)	13 (65)
Number of previous episodes (mean, s.d.)	2.11 (3.75)	2 (4.01)
Age of onset of first episode (years) (mean, s.d.)	32.11 (13.09)	31.6 (12.34)
Length of previous episodes (weeks) (mean, s.d.)	23.33 (16.91)	37.33 (27.39)
Length of current episode (weeks) (mean, s.d.)	50.65 (57.80)	42.6 (45.75)
Comorbidity (%)		
Dysthymia	4 (20)	2 (10)
Anxiety disorders	5 (25)	2 (10)
Chronic physical conditions	2 (10)	5 (25)

Table 2 Primary reasons for discontinuation

Reason for discontinuation	Nefazodone		Paroxetine	
	8 week sleep study	24 weeks continuation	8 weeks sleep study	24 weeks continuation
Completed study (%)	15 (75)	9 (45)	17 (85)	13 (65)
Non-completers (%)				
Adverse experience	4 (20)	2 (10)	1 (5)	
Lost to follow-up	1 (5)			
Lack of efficacy		2 (10)	2 (10)	3 (15)
Improvement		1 (5)		
Other known cause		1 (5)		1 (5)
Total discontinuations	5 (25)	6 (30)	3 (15)	4 (20)

described in the Method section, we separated this baseline difference from the treatment effects.

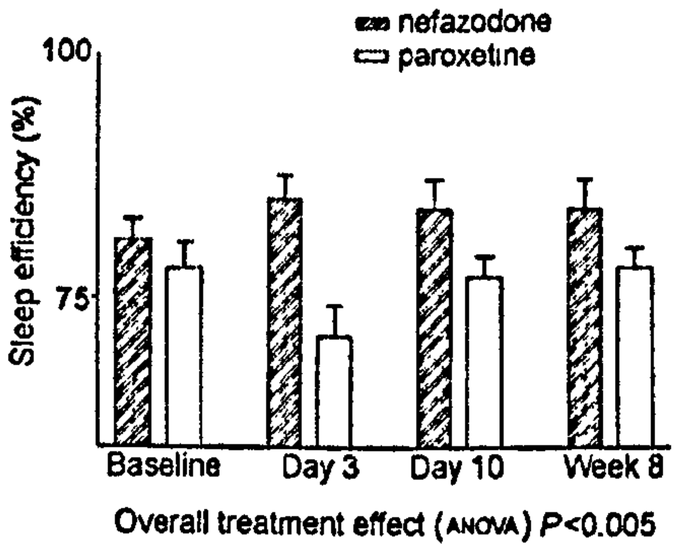
There were significant drug effects on total sleep time, sleep efficiency (see Fig. 1) and wakefulness after sleep onset, with nefazodone improving these and paroxetine worsening them early in treatment but both drug groups returning towards baseline by 8 weeks. Stage 1 sleep and number of awakenings also showed significant treatment effects and these were more obvious at 8 weeks, with both measures being increased in the paroxetine group (see Fig. 2). Number of awakenings showed a significant time × treatment effect, with the nefazodone group showing an early decrease and returning towards baseline at 8 weeks and the paroxetine group continuing to increase during treatment.

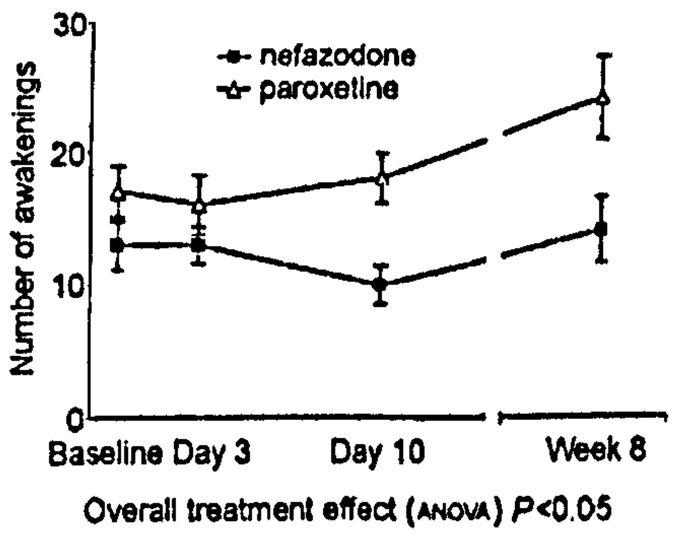
There were highly significant treatment differences on REM sleep, with paroxetine increasing REM latency (see Fig. 3) and decreasing the amount of REM throughout the 8 weeks' treatment. The nefazodone group showed a slight increase in REM and decrease in REM latency. Neither slow wave sleep nor stage 2 sleep showed significant time or group differences.

Subjective data from the SMHSQ were not distributed normally and there was a significant difference between the two treatment groups at baseline.

Changes from baseline scores were derived for all patients and these were found to be distributed normally and therefore used in subsequent testing. A significant difference was found at night 3 for sleep quality (item 5: how well did you sleep?) ($T=2.12$, d.f.=36, $P=0.04$) with the nefazodone group showing greater improvement from baseline. On the ANOVA there was a treatment effect for sleep quality ($P=0.042$) and for sleep depth ($P=0.042$) with the nefazodone group showing more improved scores on both (Table 4 and Fig. 4).

There was no significant treatment effect on the variables of LSEQ but the factor 'behaviour following wakening' showed a trend for less clumsiness and tiredness in the morning with paroxetine and more with nefazodone. The differences from baseline, however, were small. The week-by-week analysis of the sleep diary averages for sleep quality (how well I slept) and continuity (how many times did you wake up?) and the HRSD sleep items were not significantly different in the two groups.





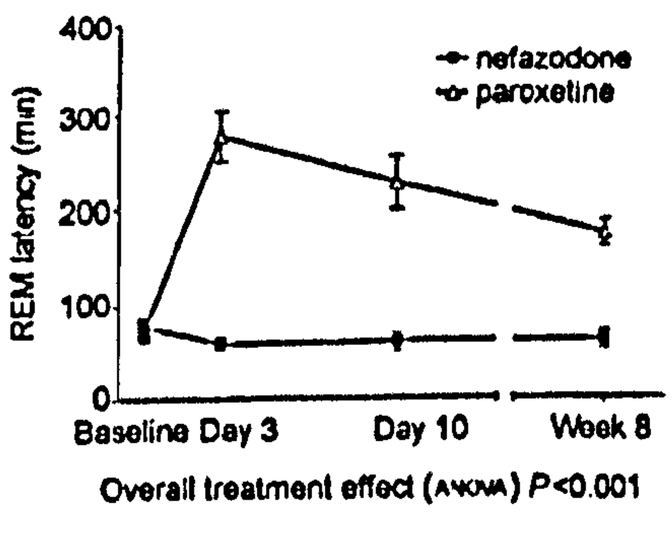


Fig. 1 Mean sleep efficiency. Error bars indicate s.e.m.

Fig. 2 Mean number of awakenings. Error bars indicate s.e.m.

Fig. 3 Mean REM latency. Error bars indicate s.e.m.

Table 3 Objective (EEG) sleep

Objective sleep measure	Nefazodone mean (s.d.)				Paroxetine mean (s.d.)				ANOVA (treatment effect)	
	Baseline *n*=19	Day 3 *n*=19	Day 10 *n*=18	Week 8 *n*=14	Baseline *n*=18	Day 3 *n*=17	Day 10 *n*=18	Week 8 *n*=16	*F*	*P*
Time in bed	474 (61)	482 (60)	466 (73)	473 (65)	479 (83)	472 (79)	458 (64)	495 (56)		
Sleep onset latency	31 (32)	33 (29)	35 (46)	20 (9)	33 (32)	55 (48)	36 (25)	41 (35)		NS
Total sleep time	383 (48)	409 (67)	389 (40)	396 (53)	370 (63)	334 (76)	352 (61)	388 (70)	5.05	0.05
% Sleep efficiency	81 (9)	85 (10)	84 (12)	84 (11)	78 (11)	71 (13)	77 (9)	78 (8)	11.49	0.005
Wake time after sleep onset	55 (42)	35 (41)	40 (40)	53 (60)	67 (58)	74 (54)	74 (52)	63 (37)	7.2	0.025
Number of awakenings[1]	13 (8)	13 (6)	10 (6)	14 (9)	17 (8)	16 (9)	18 (8)	24 (13)	7.51	0.025
% Stage 1	10 (6)	9 (8)	6 (4)	6 (4)	10 (7)	11 (8)	10 (6)	13 (7)	6.33	0.025
% Stage 2	45 (10)	46 (9)	46 (9)	46 (12)	40 (13)	45 (13)	45 (9)	40 (9)		NS
% Stage 3	7 (4)	8 (5)	9 (6)	11 (8)	7 (4)	9 (8)	8 (5)	7 (4)		NS
% Stage 4	8 (6)	6 (5)	6 (6)	6 (8)	9 (10)	10 (13)	9 (11)	6 (10)		NS
% REM	21 (6)	24 (5)	26 (8)	23 (6)	20 (7)	7 (8)	12 (6)	6 (6)	29.4	0.01
REM onset latency	78 (36)	59 (28)	61 (42)	62 (34)	73 (45)	278 (113)	227 (120)	173 (52)	133.0	0.001

NS, non-significant.
1. Time effect (ANOVA): $F=5.06$, $P=0.01$; time × treatment effect (ANOVA): $F=3.7$, $P=0.03$.

Table 4 Subjective sleep parameters (St Mary's Hospital Sleep Questionnaire). All data presented as mean (s.d.)

Variable	Nefazodone				Paroxetine			
	Baseline *n*=20	Day 3 *n*=20	Day 10 *n*=19	Week 8 *n*=14	Baseline *n*=20	Day 3 *n*=19	Day 10 *n*=18	Week 8 *n*=16
Time it took me to fall asleep (min.)	67 (54)	41 (29)	47 (38)	29 (21)	61 (48)	59 (50)	31 (22)	28 (56)
Total time I slept (min.)	335 (87)	379 (78)	375 (86)	408 (62)	336 (82)	354 (59)	395 (105)	441 (62)
Depth of sleep[1]								
(1=v. light to 8=v. deep)	3.05 (1.5)	4.1 (1.45)	4.58 (1.61)	4.54 (0.96)	3.85 (1.69)	3.95 (1.72)	4.33 (1.91)	4.31 (1.07)
How many times I woke up	3.35 (1.5)	2.7 (1.69)	1.84 (1.71)	2.29 (1.38)	2.9 (2.13)	2.84 (1.15)	2.35 (1.73)	3.06 (2.02)
How well I slept[1]								
(1=v. badly to 6=v. well)	2.65 (2.03)	3.7 (0.8)	3.63 (1.16)	4 (0.96)	3.2 (1.15)	3.37 (1.38)	3.83 (1.29)	3.94 (0.68)
How clear-headed I felt on waking								
(1=v. drowsy to 6=v. alert)	2.6 (1.27)	2.6 (0.94)	2.47 (1.12)	2.93 (1.07)	2.65 (1.35)	2.53 (1.12)	2.89 (1.02)	3.07 (1.33)
How satisfied I am with my sleep								
(1=v. unsatisfied to 5=completely satisfied)	1.85 (0.88)	2.9 (1.12)	3.06 (1.34)	3.43 (1.02)	2.3 (1.13)	2.79 (1.23)	3.33 (1.03)	3.4 (1.12)

1. Significant drug effects on ANOVA.

Analysis of antidepressant efficacy and safety

Response was defined as a 50% or greater reduction from the initial HRSD score, whereas remission was defined as a final HRSD score of 8 or less. There was no significant difference between the two medications in these variables. At week 8 (end of the sleep study), 11 patients on nefazodone and 16 patients on paroxetine were responding to treatment. At the end of the 24-week study, a total of 12 in the nefazodone group and 14 in the paroxetine group had responded to treatment, while 9 patients on nefazodone and 12 patients on paroxetine wer classified as remitters. Between 8 and 24 weeks, 2 patients in the paroxetine group had experienced a worsening.

There were no significant differences between the two drugs in HRSD, MADRS, CGI Severity and Improvement scales, either on observed data or on LOCF data. The data from HRSD scores (LOCF) are presented in Fig. 5. Data from the MADRS questionnaire, which has only one question about sleep, were as follows (observed cases): nefazodone group baseline 27.5 (s.d.=4.1), 8 weeks 13.0 (s.d.=7.7); paroxetine group baseline 27.1 (s.d.=3.5), 8 weeks 8.4 (s.d.=6.2).

There were no serious adverse events related to either of the medications. One patient on paroxetine was hospitalised for worsening of her primary diagnosis of depression and emerging suicidal ideation, following the day 3 visit. The

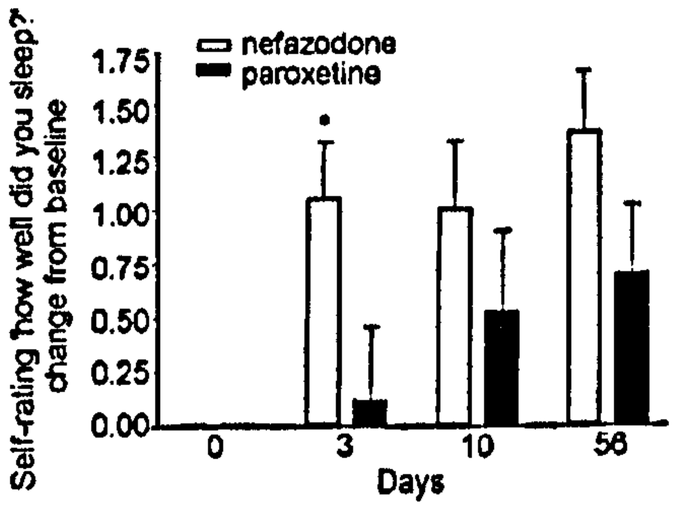


Fig. 4 Subjective sleep measures – change from baseline St Mary's Hospital Sleep Questionnaire Quality of sleep. Error bars indicate s.e.m. *$P < 0.05$.

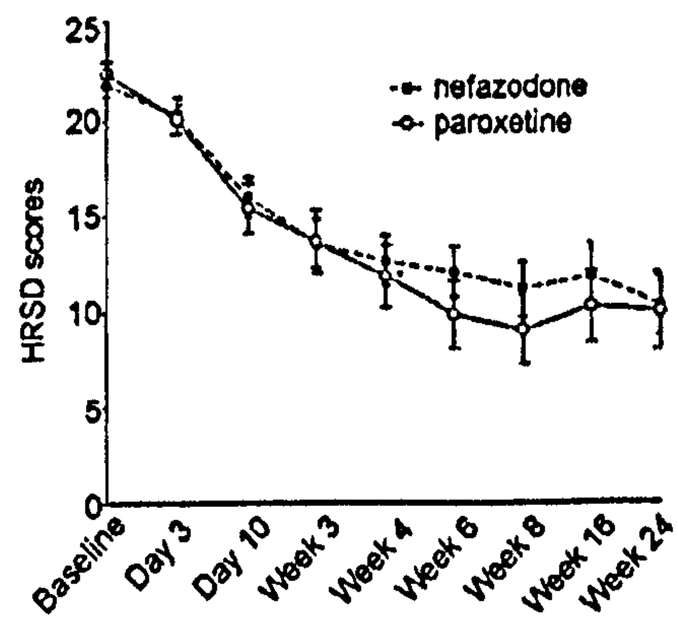


Fig. 5 Hamilton Rating Scale for Depression (HRSD) scores last observation carried forward, intention to treat. Error bars indicate s.e.m.

randomisation code was broken and the patient was continued on open-label paroxetine and made a good recovery. Table 5 shows the non-serious side-effects attributable to the medications. These were similar to those described in previous reports.

DISCUSSION

At baseline, the depressed patients in this study had disturbed sleep, as in other studies. Total sleep time and sleep efficiency were low, median REM onset latency was slightly short and stage 1 sleep was increased compared with normal sleep. Slow wave sleep, however, was higher in our study than in most sleep laboratory studies in depression, including that of Rush *et al* (1998) with nefazodone. This could reflect the use of home recordings for these patients, as we found similar baseline values in a previous study of patients with depression recorded at home. The two groups were different at baseline, with the paroxetine group having generally worse sleep. The key finding in this study was an improvement in sleep maintenance early in treatment in the nefazodone group, with sleep efficiency and total sleep time increasing and wake time decreasing, and the converse effect, i.e increased sleep disturbance, after paroxetine. This is in accordance with the previous US study (Rush *et al*, 1998) which compared nefazodone with fluoxetine. However, in contrast to that study, the differences at 8 weeks were much less marked. Only the number of awakenings and amount of stage 1 sleep were higher at this stage in the paroxetine than the nefazodone group and the sleep onset latency in the nefazodone group was shorter. It seems that paroxetine has a less disturbing effect than fluoxetine on sleep in long-term treatment, although our use of home recordings could contribute to this difference.

Table 5 Number of non-serious adverse events occurring in more than 5% of patients (% of patients reporting)

Type of adverse event	Nefazodone	*	Paroxetine	*
Stomach upset, nausea, vomiting, diarrhoea	13 (40%)	2	23 (65%)	2
Headache, migraine	15 (50%)		15 (50%)	1
Tiredness, asthenia	9 (40%)		13 (55%)	1
Drowsiness/sedation	11 (40%)	2	5 (25%)	
Dry mouth	6 (25%)		7 (35%)	
Dizziness	5 (25%)		3 (15%)	
Flu-like symptoms	2 (10%)	4	4 (15%)	
Unsteadiness, giddiness, ataxia	6 (25%)		3 (15%)	
Sweating	0		7 (35%)	
Sexual dysfunction	0		5 (20%)	
Light-headedness, spaced-out feeling	1 (5%)		4 (20%)	
Rash, itching	1 (5%)		4 (20%)	
Tremor, shakiness	0		4 (20%)	
Constipation	1 (5%)		3 (15%)	
Other (each reported in only one patient)	13	8	12	5

*Events considered by investigator at the time as unrelated to study medication.

REM sleep suppression remains marked throughout treatment with paroxetine but nefazodone has, if anything, a small non-significant promoting effect on REM, as in other studies (Sharpley *et al*, 1992). This is different from the TCAs, which produce a similar and sometimes more marked sleep promotion early in treatment but also produce a marked suppression of REM sleep.

Subjective effects

In our study, both drugs were well tolerated and equally effective in treating depression. Patients taking nefazodone reported increased subjective sleep quality and increased subjective depth of sleep as early as day 3 of treatment. The difference between the two drugs was decreased as the treatment progressed and by the end of the study was not statistically significant. This could be explained by some early sleep-promoting effect of nefazodone, or a decrease of sleep disruption caused by the SSRIs as neuroadaptive changes take place in the brain with prolonged administration and depression improves. Another possible explanation is a change in the perception and/or reporting of sleep difficulties by depressed patients as their clinical status evolves. In a previous study with fluvoxamine (Wilson *et al*, 2000), subjective complaints about poor sleep were decreased when patients improved, in spite of lack of significant changes in objective measures of sleep (polysomnography).

Comparison with other studies

The SSRIs have become a first line treatment of depression over the past decade. They offer significant advantages compared with the old compounds (TCAs and monoamine oxidase inhibitors), such as fewer side-effects and non-lethality in overdose. However, some useful properties of the TCAs, such as the promotion of sleep, do not apply to SSRIs. Indeed the SSRIs can increase wakefulness, reduce total sleep time and sleep efficiency. Generally, they have an alerting effect in acute treatment, although sleep disruption can ease with long-term treatment (Wilson *et al*, 2000). This alerting effect sometimes results in the use of additional short-term treatment with a benzodiazepine or other hypnotic, with all the well-known problems associated with such a regime. Sleep problems are very prominent in depressive illness, with up to 95% of patients with moderate to severe depression suffering one or more problems with their sleep (Thase, 1999). Therefore, new antidepressants that do not cause further sleep disruption (unlike the SSRIs) and are safe in overdose (unlike the TCAs) could offer an important advantage, especially in patients with pronounced sleep difficulties.

Pharmacological mechanisms

The main action of nefazodone is to block post-synaptic 5-HT_2 receptors (Taylor *et al*, 1995). Evidence for the involvement of 5-HT_2 receptors in depression comes from various areas of research. Although this relationship is complex and not yet very well understood, it appears that down-regulation of these receptors could be crucial for the ability of antidepressant drugs to exert their action (Attar-Lévy *et al*, 1999; Yatham *et al*, 2000), although this finding has not been replicated in all studies (Massou *et al*, 1997). The effectiveness of nefazodone has been established both in the acute and the long-term treatment of depression in a number of randomised controlled trials (Feiger *et al*, 1999; Keller *et al*, 2000). The relationship of 5-HT neurotransmission and sleep is a complex one (Sharpley & Idzikowski, 1991). SSRIs are sleep-disturbing early in treatment, presumably as a consequence of increased 5-HT function. Post-synaptic 5-HT_2 blockade, by drugs such as ritanserin, has a promoting effect on deep non-REM sleep. Trazodone, an antidepressant which shares the 5-HT_2-blocking property of nefazodone, is also sleep-promoting (Mouret *et al*, 1988).

Clinical relevance

We compared the effect of nefazodone and an SSRI on sleep of out-patients with depression, with particular emphasis on the early stages of treatment. We considered that the onset of treatment is a crucial period. The patient's morale is at its lowest and the antidepressant has not yet exerted its effect, therefore the symptoms are at their peak. Further sleep disruption, such as that caused by the SSRIs, can lead either to disaffection with the treatment and early drop-out or poor compliance, negatively affecting the overall outcome, or it could require additional treatment with a hypnotic.

Another difference with the previous study was that patients were studied in their home environment. Patients studied overnight in a sleep laboratory need a period of adjustment to the unfamiliar surroundings and this only adds to the inconveniences already produced by the

illness itself. As in our previous study, we found patients more likely to volunteer for the study once they knew that home recordings were involved.

Paroxetine was chosen as a comparator because it is the only SSRI for which sedative properties have been reported (Kerr *et al*, 1997), as opposed to the previously studied fluoxetine. As well as home-based objective sleep assessment, we also used more extensive subjective sleep measures in an attempt to clarify the effect of the two drugs in a variety of sleep parameters. The (unusual for SSRIs) sedative properties of paroxetine in some patients, which could relate to its weak anticholinergic effects, could also account for the small differences seen in this study, compared with the clear superiority of nefazodone over fluoxetine in promoting sleep, as reported by Rush *et al* (1998).

We conclude that nefazodone is an effective and safe antidepressant that could be a preferable choice over the SSRIs in patients with depression who have prominent sleep problems.

CLINICAL IMPLICATIONS

- Nefazodone significantly improved objective and subjective sleep quality early in treatment compared with paroxetine.
- Both drugs were well tolerated and seemed equally effective in treating depression.
- By 8 weeks, there was no difference in effects on sleep quality between the two drugs.

LIMITATIONS

- There was no placebo group.
- The study was powered for sleep measures, so was unable to detect clinically significant differences in antidepressant efficacy for the two antidepressants.
- The relationship between subjective and objective sleep is unclear.

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Correlation of subjective and objective sleep measurements at different stages of the treatment of depression

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Abstract

Studies of the correlation of subjective and objective sleep measures in depressed patients have produced mixed results so far. Further, they were carried out in sleep laboratories and tended to obtain one-off assessments, thus not taking into account the effect of treatment. We investigated forty (40) patients over the course of 8-week treatment of depression with either paroxetine or nefazodone. We used home polysomnography at baseline, nights 3 and 10, and week 8 of treatment, with extensive assessments of subjective sleep, the morning after each sleep recording. The patients were able to judge accurately their total sleep time and sleep onset latency, both before and during treatment. However, they were inaccurate in estimating the number of times they woke up during the night. Sleep satisfaction correlated negatively with Stage 1 sleep at baseline. Sleep quality was represented by a combination of subjective parameters measuring the ease of initiation and maintenance of sleep, and it appeared to derive from slow wave sleep and sleep continuity as seen in polysomnography. The partial discrepancy between subjective and objective measures suggests that a cognitive element is combined with the biological element to produce the sleep problems reported by depressed patients.

Keywords: Sleep onset latency (SOL); Total sleep time (TST); Stage 1 sleep; Slow wave sleep (SWS); Sleep quality; Sleep electroencephalography; Polysomnography

1. Introduction

Depression is closely associated with sleep disturbances, both in clinical (Benca et al., 1992) and epidemiological samples (Ford and Cooper-Patrick, 2001). In the clinic, over 80% of depressed patients complain of at least one of the following: difficulty with the initiation of sleep, fragmented sleep, disturbing dreams, early morning wakening, decreased amount of sleep, not feeling refreshed in the morning, and being tired during the day (Reynolds and Kupfer, 1987; Hamilton, 1989). The added importance of poor sleep is highlighted by its significant association with increased suicidality in depressed subjects (Agargun et al., 1997). The assessment of these complaints has been standardised, and a number of detailed self-report

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questionnaires are now available (Parrott and Hindmarch, 1980; Leigh et al., 1988; Buysse et al., 1989; Akerstedt et al., 1994).

Objective assessment of sleep may be provided by electroencephalographic (EEG) study of sleep (polysomnography), an established method of studying sleep architecture. It is generally well accepted by patients, whether it is performed in sleep laboratories or, more recently, at the individual's home. Studies in mood disorders confirm that several aspects of the sleep process are affected. Compared with normal controls, depressed subjects show significantly prolonged sleep latency, as well as reduced total sleep time and reduced sleep efficiency. Rapid eye movement (REM) sleep is also affected. REM latency is shortened and the duration of the first REM period is increased. The REM density over the whole night is increased and the same applies to the percentage of REM (%REM) sleep over the total sleep time. Finally, overall non-REM sleep, slow wave sleep (SWS) and the percentage of slow wave sleep (%SWS) over the total sleep time are also reduced (Benca et al., 1992). It is estimated that short REM latency, decreased SWS and increased wakefulness are present in 40–70% of depressed outpatients (Armitage et al., 1997).

While both subjective and objective measurements may be very useful in tracking the course of the illness and the treatment effects, as well as offering prognostic indicators for outcome and relapse (Kupfer et al., 1981, 1990), they often overlap in what they measure. What is not very well established is how they relate to each other, in other words, whether the subjective sleep complaints correspond to discernible alterations of sleep structure and vice versa. The implicit assumption that SWS, as seen on the EEG, corresponds to the experience of deep restorative sleep has been challenged (Armitage et al., 1997). Further, a comparison of the prevalence (cited above) of subjective and objective sleep disturbances in depressed patients indicates that the former may be more common than the latter. Indeed, it is not unusual in clinical practice to see patients complaining of poor sleep without any abnormal polysomnographic findings. In a study by Mayers et al. (2003), depressed patients experienced more 'sleep distress' than healthy individuals even though their estimates of sleep disturbance were similar to those of controls.

Previous studies of the correlation of subjective and objective sleep measures in depression have produced mixed results. Some indicate that the correlation may not be good (Lee et al., 1993; Rotenberg, 1993; Rotenberg et al., 2000), while others have suggested the opposite (Hemmeter et al., 1995; Armitage et al., 1997). We reasoned that this discrepancy might be the result of methodological issues in these studies (Table 1). Some had a rather small sample size or the sample did not consist entirely of depressed patients. The subjective measures used for the comparisons were often rudimentary. On occasions, formal statistical correlations were not attempted and the researchers offered only casual comments on the direction of the comparisons, because this was not the main aim of their study. Control groups were used in some studies but not in others. Finally, some only provided snapshot assessments, and they did not study the stability of the correlations over a period of time. Therefore, we sought to compare subjective and objective sleep measures in a large enough sample, using detailed subjective measurements and repeating the assessments a number of times during treatment.

2. Methods

This was part of a double blind, randomised, parallel group, 8-week study of 40 outpatients (23 females, 17 males) with moderate to severe depression, without psychotic features. The primary objective of the trial was to compare the effects of nefazodone ($n=20$) and paroxetine ($n=20$) on sleep and mood, and the local Ethics Committee approved the study. The patients fulfilled DSM-IV criteria for major depression (American Psychiatric Association, 1994) and had a Hamilton Depression Rating Scale (HAM-D) score of 18 or over (Hamilton, 1960) (Table 2). The selective serotonin reuptake inhibitors (SSRIs), like paroxetine, have become the mainstay of the pharmacological treatment of depression in recent years. Some of the newer compounds, like nefazodone, claim advantages over the SSRIs in some symptom areas,

Table 1
Summary of previous studies assessing the correspondence of subjective and objective sleep measures

	Diagnosis	Sample size	Control group	Subjective measures	Assessments	Outcome
Rotenberg (1993)	Mixed	75 (28 depressed)	15 (not matched)	Depth of sleep, sleep denial, mental activity before enforced awakening	Baseline only	Patients not able to judge sleep depth accurately
Lee et al. (1993)	Depression	15	15 (age and sex matched)	PSQI	Baseline and after remission, with medication discontinued	No patient-control differences in objective measures. Improvement of subjective sleep quality contrasted with stability of objective measures
Hemmeter et al. (1995)	Depression	18	No	Total sleep time, sleep onset latency, number of awakenings, depth of sleep, refreshedness	Baseline and after 7 nights of treatment	Changes in objective sleep variables in parallel with the subjective variables
Armitage et al. (1997)	Depression	52	49 (not matched for age)	Time in bed, total sleep time, sleep onset latency, number of awakenings, sleep quality, restfulness of sleep	Baseline only	Patients differed from controls only in sleep efficiency. Subjective and objective sleep measures correlated in both groups, except for number of awakenings
Rotenberg et al. (2000)	Depression	30	10 (not matched)	Sleep duration, sleep delay, number of awakenings	Baseline only	Patients differed from controls in a number of objective measures. In patients, no subjective/objective correlations

PSQI: Pittsburgh Sleep Quality Index.

including sleep. However, head to head comparisons testing these claims are still scarce. Further details of the methodology with regards to the patient population, the study design and medication and the treatment outcome are given elsewhere (Hicks et al., 2002).

Table 2
Basic demographic and clinical characteristics of the sample

	Nefazodone ($n=20$)	Paroxetine ($n=20$)
Age in years (mean±S.D.)	42.7 (±11.9)	42.9 (±10.1)
Sex: male/female	8/12	9/11
Medication daily dose: mean (±S.D.)	495 mg (±82.6)	29.5 mg (±8.9)
HAM-D at baseline (±S.D.)	21.8±2.6	22.4±2.7
HAM-D at week 8 (±S.D.)	11.2±6.5	9.0±7.8
Responders by 8 weeks	12	16

S.D.: standard deviation.

Polysomnography was performed on the patients at home, using the Medilog 9200 (Oxford Instruments Medical, Old Woking) ambulatory monitoring system, at baseline, on nights 3 and 10, and at 8 weeks of antidepressant treatment. Subjective assessments of sleep, using the St. Mary's Hospital Sleep Questionnaire (SMHSQ) (Leigh et al., 1988), were obtained on the morning after each recording. The Leeds Sleep Evaluation Questionnaire (LSEQ) (Parrott and Hindmarch, 1980) was also administered the morning after nights 3 and 10 and at 8 weeks. The combined score (range: 0–6) of the three sleep items of the HAM-D, covering initial, middle and late insomnia, were also compared with objective sleep measures. During the first 3 weeks of the study, patients kept a daily diary of sleep quality and number of awakenings using visual analogue ratings. Clinical assessments of depression, using the HAM-D, the Montgomery–Åsberg Depression Rating Scale (MADRS) (Montgomery and Åsberg, 1979) and the Clinical Global Impression Scales (CGI) (Guy, 1976), were performed on the days preceding the sleep recordings, as well as other regular intervals.

Sleep was scored automatically with visual correction according to established criteria (Rechtschaffen and Kales, 1968) by an experienced sleep scorer (JAH) who was blind to treatment and illness state. The parameters derived from the sleep EEGs were: staging time—the interval between the time the patients closed their eyes at night and when they opened them and started to move around in the morning; total sleep time (TST)—the time in all stages of sleep; sleep efficiency—expressed as %TST/staging time; number of awakenings—counting those longer than 16 s in duration; sleep onset latency (SOL)—time from the patient first closing his eyes to the first 2 min of Stage 2 sleep; duration of Stages 1 to 4 and REM sleep, as well as REM onset latency—the time to the onset of Stage 2 sleep to the first 2 min of REM sleep; and wakefulness after sleep onset—the total time spent awake after sleep onset.

The SMHSQ consists of 14 items, scored in variable format. It covers: timing of sleep over the last 24-h period; presence or absence and length of initial insomnia; depth of sleep; number of awakenings; total amount of sleep; presence or absence of early morning wakening; level of clear-headedness the following morning; and overall quality and satisfaction with the sleep of the night before the assessment. The LSEQ consists of 10 items comparing the experience of sleep the night before with that before the onset of treatment. These items are scored on a 100-mm visual analogue scale and cover: relative ease of getting to sleep; number of awakenings; restless/restful sleep; relative ease of waking up in the morning; feelings of tiredness/alertness; and sense of balance and co-ordination upon waking up.

3. Results

The demographic and clinical characteristics of the population are summarised in Table 2. Of the total sample, 36 patients (18 in each treatment group) provided technically valid polysomnography data for at least three sleep recordings, including baseline. All 36 patients also provided valid subjective data for the mornings after each one of the sleep recordings that were analysed. Of the 36 patients, eight were withdrawn from treatment after the third and before the fourth and final sleep recording at week 8. Reasons for discontinuation were: side effects (nefazodone=4, paroxetine=1); lost to follow up (nefazodone=1); and lack of efficacy (paroxetine=2). A summary of objective polysomnographic variables is given in Table 3, and correlations between subjective and objective measures are shown in Table 4. Fig. 1 shows the diary ratings of sleep. Patients in the paroxetine group rated their sleep as worse on the polysomnography nights compared with the nights before and after polysomnography.

3.1. Sleep initiation and maintenance

There was a significant correlation between patients' estimate of their TST and actual TST. This was maintained at all time points during treatment. More patients underestimated than overestimated their sleep (Fig. 2) at baseline. There was no obvious alteration in the under- or overestimation of sleep during the course of the study.

Table 3
Polysomnographic variables

	Nefazodone				Paroxetine			
	Mean ± S.D.				Mean ± S.D.			
	Baseline	Day 3	Day 10	Week 8	Baseline	Day 3	Day 10	Week 8
Sleep onset latency (min)	31±32	33±29	35±46	20±9	33±32	55±48	36±25	41±35
Total sleep time (min)	383±48	409±67	389±40	396±53	370±63	334±76	352±61	388±70
Number of awakenings	13±8	13±6	10±6	14±9	17±8	16±9	18±8	24±13
WASO (min)	55±42	35±41	40±40	53±60	67±58	74±54	74±52	63±37
Sleep efficiency (%)	81±9	85±10	84±12	84±11	78±11	71±13	77±9	78±8
Stage 1 sleep (min)	40±26	38±21	27±18	28±20	42±36	46±31	45±27	57±33
Stage 2 sleep (min)	182±57	204±49	178±44	197±55	171±8	184±3	186±4	182±12
Stage 3 sleep (min)	30±17	36±8	40±26	47±32	32±19	34±9	33±21	34±17
Stage 4 sleep (min)	31±8	27±24	25±6	27±25	39±9	37±41	36±9	36±8
REM sleep (min)	87±30	102±35	105±43	98±28	87±34	33±38	49±27	79±33
REM onset latency	78±36	59±28	61±42	62±34	73±45	278±113	227±120	173±52

There was also a significant correlation between subjective SOL and SOL derived from EEG at nights 3 and 10. This correlation was near significance at baseline but absent at week 8. At day 3, there were negative correlations between SOL and morning clear-headedness and 'hangover' feeling; the shorter the sleep latency, the more hangover the patients experienced the following morning.

There was very little correlation between subjective and objective measures of awakening. The objective and subjective number of awakenings only correlated at week 8. The former also correlated negatively with subjective sleep time at week 8, while the latter correlated with wake after sleep onset at day 10.

3.2. Sleep architecture

There was a negative correlation between sleep satisfaction and Stage 1 sleep at baseline. Otherwise, Stage 1 and Stage 2 sleep did not correlate with any subjective sleep measures at any other time point.

There was a good correlation between several subjective measures of sleep quality and amount of SWS at day 10. We investigated this further by combining (adding the scores) 'depth of sleep', 'how well slept' and 'how satisfied with sleep' of the SMHSQ. This composite index of sleep quality correlated strongly (for both drugs) with increase in SWS from baseline (see Fig. 3).

Few correlations of REM with subjective aspects of sleep emerged. REM sleep was correlated with subjective sleep time on day 3. REM onset latency was negatively correlated with awakenings and worse sleep on HAM-D at baseline. However, inspection of the individual data indicated that this correlation was mainly based on three outliers who had extremely short REM latencies and a high number of awakenings.

There were no significant differences on any of the correlations according to gender. Fig. 4 shows the relationship between subjective sleep quality and objective time spent awake during the night according to gender. It can be seen that there are

Table 4
Significant correlations between objective and subjective sleep measures (Spearman rank test, $P<0.05$)

Subjective measures	Objective measures: TST	SOL	WASO	No of wakes	Sleep efficiency	Stage1	Stage 2	SWS	REM	ROL
SMHSQ										
Subjective sleep latency		3 10								
Depth								10		
Number of awakenings			10	8w				10–		
Sleep satisfaction					8w	B–		10		
Subjective sleep time	B 3 10 8w			8w–					3	
Sleep quality								10		
Morning clear-headedness		3–*								
Awakenings										B–
HAM-D sleep items										B– 3–
LSEQ										
Getting to sleep (worse)					3– 10–			10–		
Quality of sleep (worse)	3–									
Morning 'hangover'		3*								

All patients: B = baseline, 3 = day 3, 10 = day 10, 8w = week 8 (– is negative correlation, * is confined to the nefazodone group). SMHSQ: St Mary's Hospital Sleep Questionnaire; HAM-D: Hamilton Depression Rating Scale; LSEQ: Leeds Sleep Evaluation Questionnaire; TST: Total sleep time; SOL: Sleep onset latency; WASO: Wake after sleep onset; SWS: Slow wave sleep; REM: Rapid eye movement sleep, ROL: REM onset latency.

a few men who spent long periods awake but rated their sleep no worse than others with less disturbed sleep.

4. Discussion

In measures of sleep initiation and maintenance, our sample produced a mixed picture of correspondence of objective and subjective measures. We found that despite a tendency to underestimate their sleep, there was a good objective/subjective correlation of TST, both before and during treatment. Further, self-assessment of SOL was significantly correlated with the EEG measure at nights 3 and 10, and almost significantly so at baseline. The absence of correlation at week 8 could be explained by the effect, the outcome of treatment on the patients. Those taking nefazodone were all clustered at low SOL scores, while the ones taking paroxetine were spread out, so there was not enough overall variance of the data for a significant correlation to emerge. At baseline, our results are in accordance with those of Armitage et al. (1997), who also found a good correlation of objective and subjective TST and SOL before treatment, but not with those of Rotenberg et al. (2000), who found no such correlation. It should be noted here that our study was based on home recordings while the other two used laboratory recordings. The main difference between the two methods in the context of the above measurements is that laboratory recordings normally start measuring time in bed when lights go out, while in home recordings the starting point is when the subject closes his/her eyes.

However, the number of wakes only correlated after 8 weeks of treatment. At baseline, neither Armitage et al. (1997) nor Rotenberg et al. (2000) found a correlation between subjective and objective number of awakenings. Other studies have come to the same conclusion (Monk et al., 1994; Mayers et al., 2003). So, it can be said with some certainty that depressed patients are not accurate in judging the number of times they wake up at night. One possible explanation is that the appreciation of this particular aspect of sleep is disturbed by acute illness and returns to normal following treatment, as evidenced by the correlation found after 8 weeks of treatment in our sample. Another parameter to be taken into account here is the length of what constitutes a polysomnographic 'wake'. This measure differs from study to study and it is perhaps set arbitrarily. For example, it was >16 s in our study and >30 s in the Armitage et al. (1997) study. It could be that this level is too short to be perceptible and that in the future one should ideally control for different durations to find out what the best discriminatory level between illness and normality is. It is also known that depressed patients sometimes report that they had barely slept despite polysomnographic evidence to the opposite. As Rotenberg et al. (2000) commented, if one does not realise his or her previous sleep, one is then also unable to realise

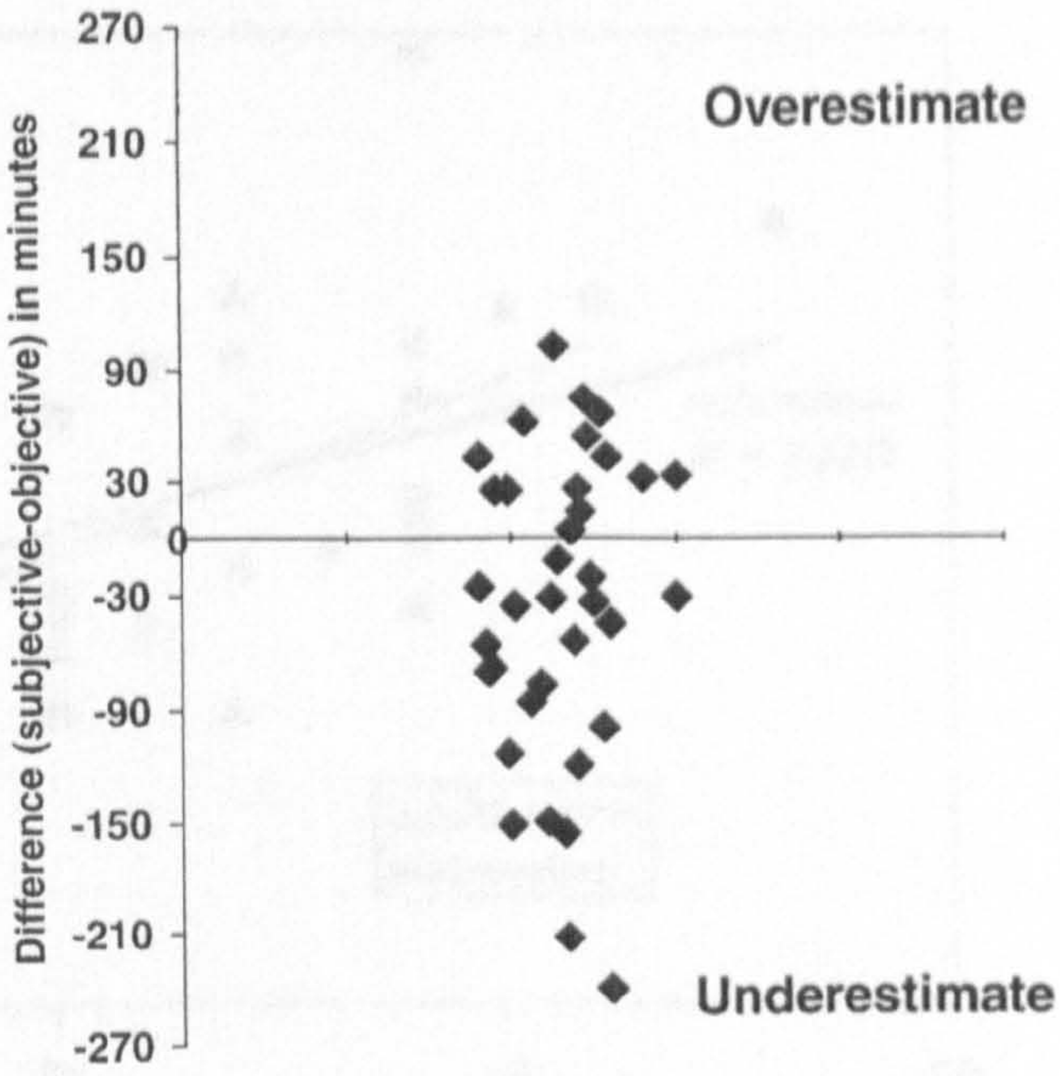

Fig. 2. Subjective and objective estimates of sleep time at baseline. Each symbol is an individual patient.

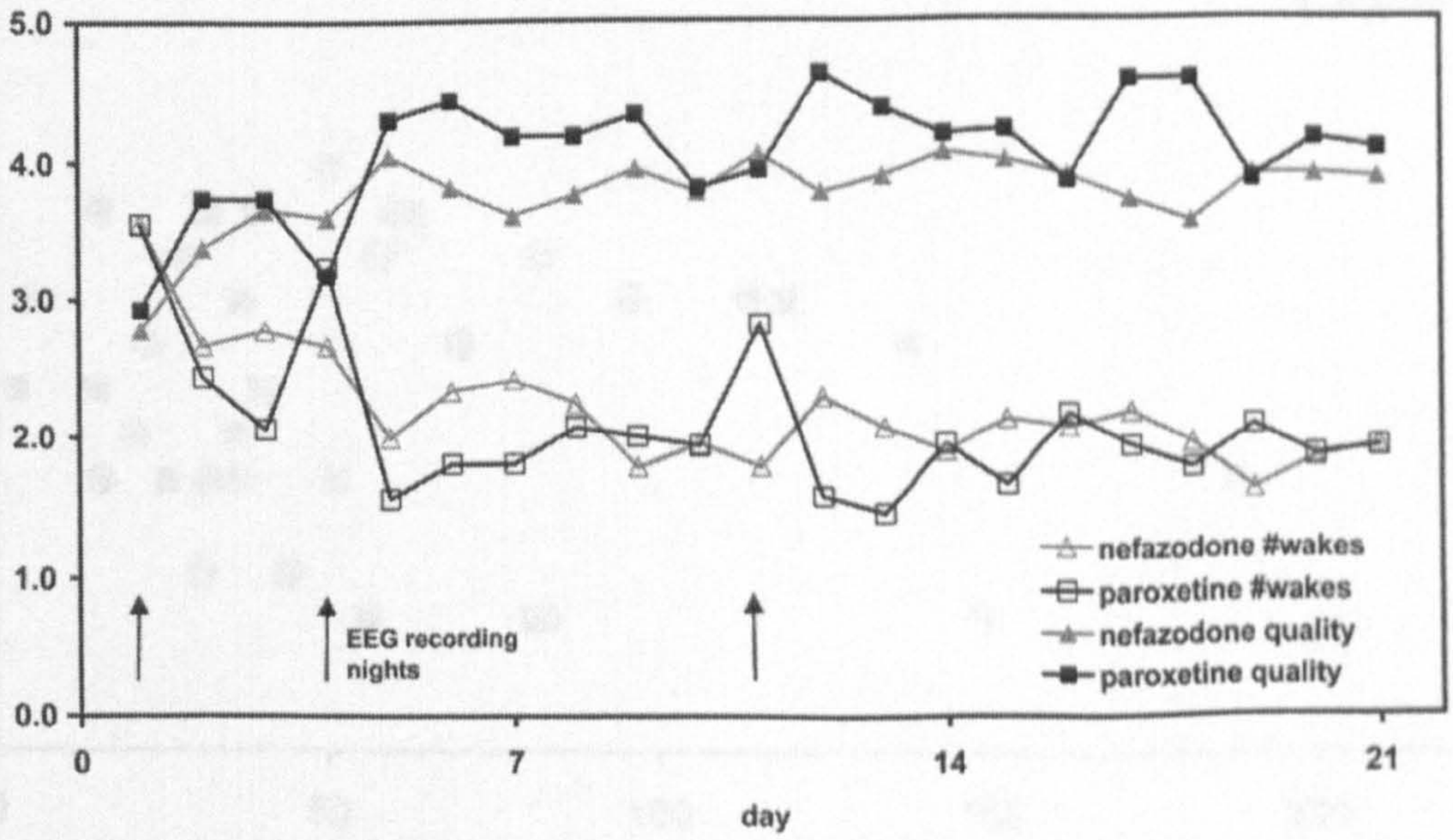

Fig. 1. Mean sleep diary ratings for quality of sleep and number of awakenings. Patients rated how well they slept the night before (range: 1=very badly to 6=very well) and estimated the number of times they woke up (range: 0=none at all to 7=more than six times). Ratings are worse on recording nights in the paroxetine group.

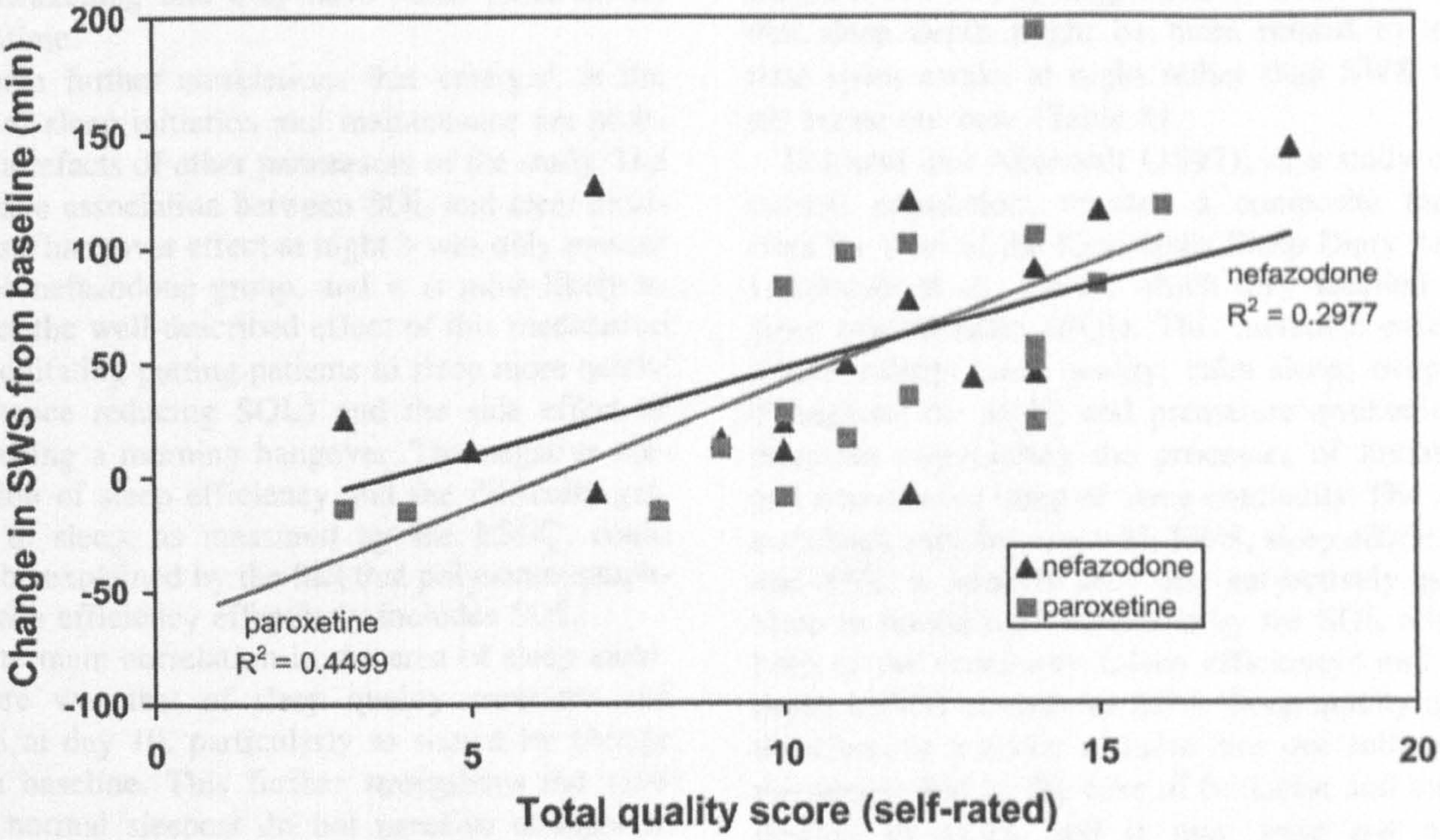

Fig. 3. Change in slow wave sleep from baseline at day 10 vs. subjective sleep quality.

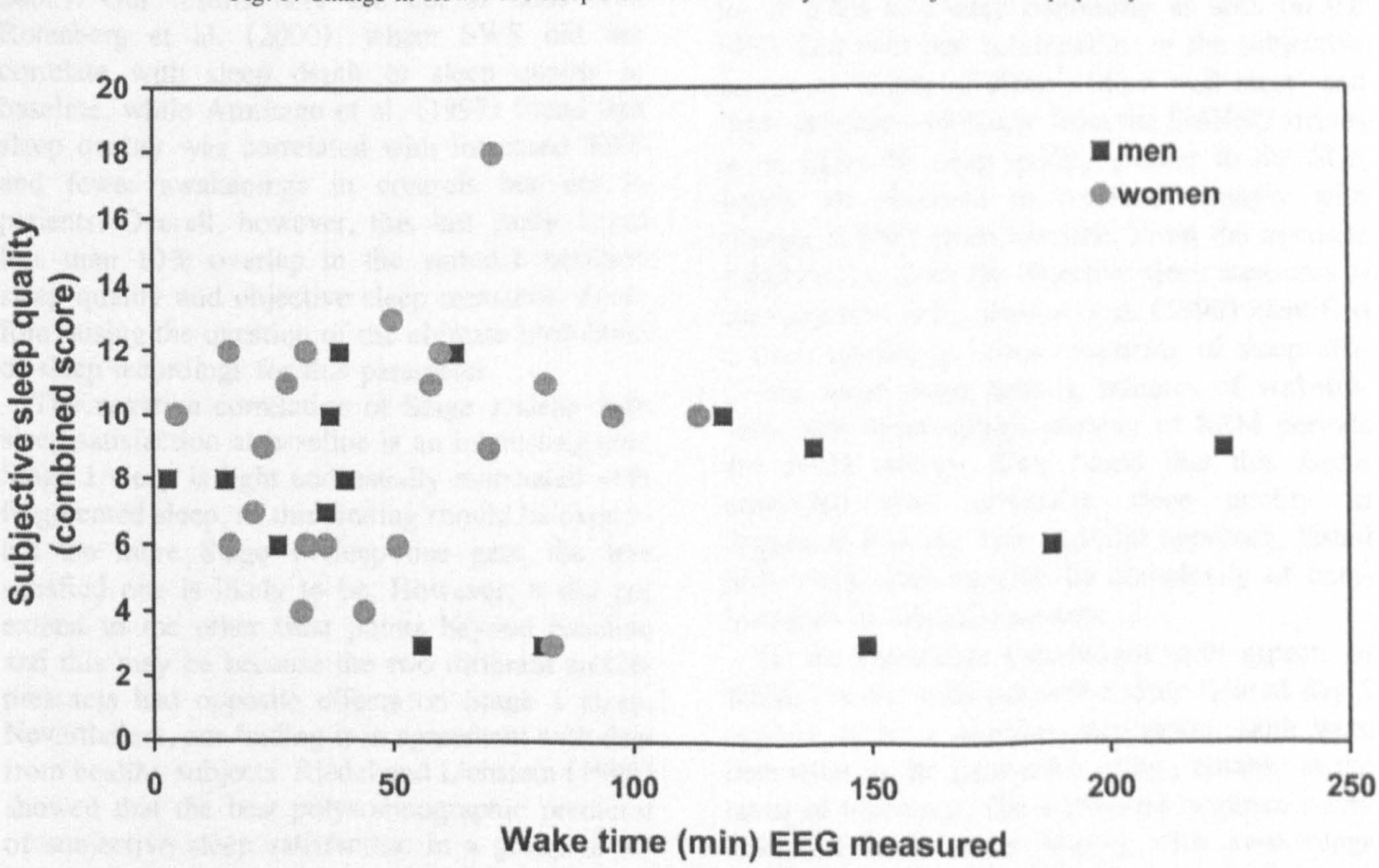

Fig. 4. Correlation between sleep quality (combined score) and EEG wake time. Results shown by gender.

the awakening that may have taken place in the meantime.

Some further correlations that emerged in the area of sleep initiation and maintenance are probably artefacts of other parameters of the study. The negative association between SOL and clear-headedness/hangover effect at night 3 was only present in the nefazodone group, and it is most likely to reflect the well-described effect of this medication of facilitating putting patients to sleep more quickly (hence reducing SOL) and the side effect of producing a morning hangover. The negative correlation of sleep efficiency and the difficulty getting to sleep, as measured by the LSEQ, could also be explained by the fact that polysomnographic sleep efficiency effectively includes SOL.

The main correlation in the area of sleep architecture was that of sleep quality measures and SWS at day 10, particularly as shown by change from baseline. This further strengthens the view that normal sleepers do not perceive changes in SWS while the poor sleepers may (Viola et al., 2002). Our results here are not at odds with Rotenberg et al. (2000), where SWS did not correlate with sleep depth or sleep quality at baseline, while Armitage et al. (1997) found that sleep quality was correlated with increased SWS and fewer awakenings in controls but not in patients. Overall, however, this last study found less than 10% overlap in the variance between sleep quality and objective sleep measures, therefore raising the question of the ultimate usefulness of sleep recordings for this parameter.

The negative correlation of Stage 1 sleep with sleep satisfaction at baseline is an interesting one. Stage 1 sleep is light and usually associated with fragmented sleep, so this finding should be expected: the more Stage 1 sleep one gets, the less satisfied one is likely to be. However, it did not extend to the other time points beyond baseline and this may be because the two different antidepressants had opposite effects on Stage 1 sleep. Nevertheless, our finding is in agreement with data from healthy subjects. Riedel and Lichstein (1998) showed that the best polysomnographic predictor of subjective sleep satisfaction in a group of 47 older healthy adults was the depth of sleep, expressed as decreased Stage 1 and increased Stages 3 and 4. The suggestion of Bonnet (1993) that sleep depth might be more related to total time spent awake at night rather than SWS was not borne out here (Table 4).

Keklund and Akerstedt (1997), in a study of a normal population, wrested a composite factor from the total of the Karolinska Sleep Diary items (Akerstedt et al., 1994), which they labelled the sleep quality index (SQI). This included: ease of falling asleep; sleep quality; calm sleep; sleeping throughout the night; and premature awakenings, therefore representing the processes of initiating and maintaining sleep or sleep continuity. The SQI correlated significantly with SWS, sleep efficiency and TST. It appears then that subjectively good sleep in normals, as measured by the SQI, relates both to the continuity (sleep efficiency) and the depth (SWS) of sleep in EEG. Sleep quality may, therefore, be a matter of more than one subjective parameter, that is, the ease of initiation and maintenance of sleep, and it may arise out of a combination of objective parameters, being a matter of SWS and sleep continuity as seen on the EEG. Our post hoc combination of the subjective scores of 'depth of sleep', 'how well slept' and 'how satisfied with sleep' from the SMHSQ arrives at an index of sleep quality similar to the SQI, which we observed to correlate strongly with change in SWS from baseline. From the opposite direction, i.e. from the objective sleep measures to the subjective ones, Buysse et al. (1998) identified a sleep continuity factor consisting of sleep efficiency, sleep onset latency, minutes of wakefulness, time spent asleep, number of REM periods and REM latency. They found that this factor correlated with subjective sleep quality in depressed women. This factorial approach, tested both ways, may unravel the complexity of combinations of related measures.

Of the significant correlations with aspects of REM, the one with subjective sleep time at day 3 appears to be a spurious association. Both were decreased in the paroxetine group, notably at the onset of treatment. The significant negative correlation of REM onset latency with awakenings could be partly explained by the fact that both increased wakefulness and decreased REM latency

commonly occur in depression, and indeed this was the case in our study.

What is the meaning of the (partial) discrepancy between objective and subjective measures of sleep? Traditionally, sleep disturbance is considered as one of the 'vegetative' symptoms of depression that is thought to have a strong biological underpinning. However, if it were not entirely biological in its element, one would not expect it to be accurately measured through EEG alone. Sleep disturbance may be a combination of biological and cognitive elements, the latter being an aspect of the well-known pervasive 'gloom' scenario of depression (Lee et al., 1993). Indeed, these authors provided further evidence supporting this idea. In their sample, improvement in subjective sleep quality was reported after remission, even in the absence of changes in polysomnography, showing that objective and subjective measures do not change in parallel and therefore may represent different elements. Such an outcome also argues for the need to use both subjective and objective methods in the assessment of sleep in depression. Subjective measures may be more valuable markers for the short-term clinical evaluation of the condition while EEG measures may have significance in understanding the long-term picture of the biological recovery of the patient.

The composition of the samples may offer some explanation with regards to the discrepant results between the various studies. Depression is a syndrome that encompasses many different symptoms and various degrees of severity. Are the samples in our study and the studies mentioned above typical in their sleep profile of the findings in depression (Benca et al., 1992)? In the Armitage et al. (1997) study, patients did not differ at baseline from controls on REM latency or %SWS. Only sleep efficiency differentiated between the two groups. This indicates that their sample was not very typical of depression, at least in sleep profile. It also argues for the inclusion of a proper control group in these studies. The same applied to the Lee et al. (1993) study, where patients at baseline only differed from controls in one measure: SOL. This in turn could explain why there is no difference between pre- and post- treatment polysomnography in this study, while subjective measures of sleep changed: the underlying sleep was not at the pathological end of the spectrum. In contrast, the patients in the Rotenberg et al. (2000) study, the one that showed the least correlation between subjective and objective measures so far, had a sleep profile that resembled more closely the typical one of depression. However, good correlation cannot be explained by these baseline characteristics of the sample alone, since our patients (before treatment) had low sleep efficiency and high waking after sleep onset compared with normal subjects.

Some limitations of our approach have been highlighted earlier in the text, notably the absence of a control group. The pre-planned inclusion of patients with a typical depression sleep profile may be desirable but it is not feasible, since recruitment is based on clinical presentation rather than polysomnographic findings. Further, if only patients with a specific sleep profile were included, variability of the data would have been much reduced and the sample would have been biased.

Subjectively the paroxetine-treated patients rated their sleep as worse on the EEG nights, but the nefazodone group appeared to notice no difference, which implies a protective role for nefazodone. This may have affected the correlations in that the EEG nights may not have been typical. However, the differences were small and unlikely to obscure large correlations. Finally, in this study we did not control for sleep apnoea, periodic leg movement or bruxism, although there was no evidence of these in the recordings.

At the heart of the comparison of subjective and objective sleep estimates lie the questions, succinctly articulated by Rotenberg et al. (2000): Is subjective estimation of sleep directly related to any corresponding or non-corresponding objective sleep variables? And is it possible to predict specific alterations of sleep structure from the subjective sleep complaints? It is not inconceivable that objective and subjective assessments of sleep quality, despite the fact that they often carry labels that imply direct relationship or equivalence, may relate to different parameters (Armitage et al., 1997). On balance, it appears that some measures of sleep continuity, such as TST and SOL correlate well between subjective and objective assessments

in depressed patients, therefore indicating a direct relationship. A notable exception here is the number of awakenings, which the patients appear unable to estimate accurately. The picture with respect to sleep quality and sleep architecture is somewhat more complicated. It seems likely that sleep quality is represented by a combination of more than one subjective sleep parameter, those of initiation and maintenance of sleep, which probably correspond to a combination of objective parameters, namely SWS and sleep continuity. Treatment and change of clinical status did not appear to have a huge influence in the relationship between subjective and objective measures, indicating that in our group they mostly co-vary.

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